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ABUSE AND FATAL POISONINGS INVOLVING PRESCRIPTION OPIOIDS

Revelations from postmortem toxicology

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ACADEMIC DISSERTATION

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THESIS AT A GLANCE

Study	Aim	Methods	Main findings
I	To compare profiles of different opioids between opioid poisonings and other opioid-related deaths.	Postmortem database study from 2000-2008, comprising 1,363 opioid-positive cases aged 14 to 44 related to buprenorphine, codeine, methadone, and tramadol.	Codeine and tramadol poisonings, as well as methadone and buprenorphine poisonings, were mutually similar. Codeine and tramadol concentrations were higher in fatal poisonings than in other deaths. Codeine, tramadol, and buprenorphine poisonings involved more additional benzodiazepines than did other deaths.
II	To assess the role of buprenorphine concentrations and benzodiazepine findings in buprenorphine deaths.	Postmortem database study from 2000-2008, comprising 391 buprenorphine-related cases, deceased aged 14 to 44.	Buprenorphine deaths were accidental polydrug poisonings with low drug concentrations. Benzodiazepines and alcohol were commonly associated findings in buprenorphine-related deaths. The buprenorphine/norbuprenorphine ratio may help in distinguishing fatal poisonings from other buprenorphine-related deaths.
III	To reveal the proportion of abuse and differences between abuser profiles of the most common prescription opioids in Finland.	Postmortem database study from 2010-2011, comprising 2,088 cases positive for buprenorphine, codeine, fentanyl, methadone, tramadol, or oxycodone.	At least 0.5% of deaths in Finland involved prescription opioid abuse. Every opioid showed certain extent of abuse while abuse and fatal poisonings were most common among men aged 20 to 49. Methadone and buprenorphine involved predominantly abuse, and abuse of tramadol was also prominent.
IV	To estimate the proportion of pregabalin and gabapentin abuse in relation to their total use.	Postmortem database study from 2010-2011, comprising 316 pregabalin and 43 gabapentin cases.	Pregabalin showed a considerable amount of abuse, especially among those deceased aged <50. Opioids findings characterised gabapentinoid-abuser deaths. Pregabalin and gabapentin abuse may be fatal, especially when combined with opioids.
V	To differentiate therapeutic use of buprenorphine-naloxone co-formulation from its parenteral abuse using urine drug measurements.	Clinical laboratory data analysis study including 40 consecutively collected samples from 32 patients in opioid maintenance treatment.	Positive urine buprenorphine without naloxone suggested use or abuse of buprenorphine. During maintenance treatment with buprenorphine-naloxone, all urine samples included some naloxone. High naloxone/buprenorphine concentration ratio in urine may act as an abuse indicator of buprenorphine-naloxone co-formulation.
VI	To assess the role of parenteral buprenorphine-naloxone co-formulation in buprenorphine-related deaths.	Postmortem database study from 1/1/2010-30/6/2011 comprising 225 buprenorphine abusers.	Postmortem buprenorphine-related cases were assessed based on the criteria established in V. Many poisonings by parenteral buprenorphine-naloxone abuse were disclosed. Abuse of the co-formulation may be even more fatal than abuse of buprenorphine.

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ABBREVIATIONS

ADHD	attention-deficit hyperactivity disorder
BNX	buprenorphine-naloxone coformulation
BPN	buprenorphine
CNS	central nervous system
CYP	cytochrome P450
DDD	defined daily dose
ECD	electron capture detection
EDDP	2-ethylidene-1,5-dimethyl-3,3-diphenylpyrrolidine
EDMP	2-ethyl-5-methyl-3,3-diphenyl-1-pyrroline
GABA	gamma-aminobutyric acid
GAD	generalised anxiety disorder
ICD	International Classification of Diseases
LC	liquid chromatography
LC-TOFMS	liquid chromatography time-of-flight mass spectrometry
MS	mass spectrometry
MS/MS	tandem-mass spectrometry
NX	naloxone
NMDA	<i>N</i> -methyl-D-aspartate
NOR	norbuprenorphine
NPD	nitrogen phosphorus detection
ODT	<i>O</i> -desmethyltramadol
OMT	opioid maintenance treatment
ORL1	opioid-receptor-like1
PMR	postmortem redistribution of drugs
PRG	pregabalin
SNRI	selective serotonin-noradrenaline-reuptake inhibitor
SSRI	selective serotonin-reuptake inhibitor
T _½	half-life
TOF	time of flight
V _d	volume of distribution
WHO	World Health Organization

ORIGINAL PUBLICATIONS

The thesis is based on the following articles, in the text referred to as Roman numerals **I-VI**:

- I** M. Häkkinen, T. Launiainen, E. Vuori, I. Ojanperä, Comparison of fatal poisonings by prescription opioids, *Forensic Sci Int* 222 (2012) 327-331.
- II** M. Häkkinen, T. Launiainen, E. Vuori, I. Ojanperä, Benzodiazepines and alcohol are associated with cases of fatal buprenorphine poisoning, *Eur J Clin Pharmacol* 68 (2012) 301-309.
- III** M. Häkkinen, E. Vuori, I. Ojanperä, Prescription opioid abuse by representative postmortem toxicology, *Forensic Sci Int* 245 (2014) 121-125.
- IV** M. Häkkinen, E. Vuori, E. Kalso, M. Gergov, I. Ojanperä, Profiles of pregabalin and gabapentin abuse by postmortem toxicology, *Forensic Sci Int* 241 (2014) 1-6.
- V** P. Heikman, M. Häkkinen, M. Gergov, I. Ojanperä, Urine naloxone concentration at different phases of buprenorphine maintenance treatment, *Drug Test Anal* 6 (2014) 220-225.
- VI** M. Häkkinen, P. Heikman, I. Ojanperä, Parenteral buprenorphine-naloxone abuse is a major cause of fatal buprenorphine-related poisoning, *Forensic Sci Int* 232 (2013) 11-15.

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ABSTRACT

Opioids are the most important drugs causing fatal poisonings. Determining whether an opioid death was poisoning may, however, be difficult even if involving appropriate toxicological laboratory investigation. Apart from heroin, little statistically significant data-analysis is available for interpretation of blood concentrations of opioids from various types of post-mortem cases. Tolerance, route of administration, and delay of death after drug administration all influence postmortem drug concentrations. In this thesis, quantitative blood concentration data extracted from the high-quality Finnish postmortem toxicology database was the investigative tool to overcome this problem.

Opioid deaths typically involve drug abuse, and suspected drug-abuser deaths must, by Finnish law, undergo medico-legal examination. Medico-legal autopsy in these cases includes comprehensive drug screening and, based on its results, more specific drug quantification. This thesis combined concentration data stored in the postmortem toxicology database with information from death certificates issued by forensic pathologists to allow statistical comparisons between drug poisonings and other deaths, as well as between drug abusers and other users. Concentration data mainly involved drug concentrations in postmortem femoral blood, but drug concentrations in urine and parent drug/metabolite concentration ratios also allowed assessment of buprenorphine, codeine, and tramadol deaths.

Opioid poisonings proved to be mainly unintentional polydrug poisonings, regularly involving benzodiazepines, gabapentinoids, and other psycholeptics. Buprenorphine and methadone blood concentrations in fatal poisonings remained within their therapeutic ranges, and these two opioids involved mostly abuse. Concentrations of the weak opioids tramadol and codeine were above their therapeutic ranges both in abuser cases and in fatal poisonings. Tramadol abuse was common but abuse of oxycodone, fentanyl, and codeine was rather low compared to their therapeutic use. Abuse of the gabapentinoids pregabalin and gabapentin was strongly associated with opioid abuse, and compared to gabapentin abuse, pregabalin abuse was proportionally more frequent.

To prevent parenteral buprenorphine abuse, opioid maintenance treatment applied a combination product of buprenorphine-naloxone. This combination product is, however, abused as well, and monitoring its abuse is challenging. In this study, urine samples collected from living patients at different phases of opioid maintenance treatment supplemented the postmortem data. Based on the criteria established with these patients, combined with postmortem data and proper background information, a urine concentration limit was estimated for suspected parenteral abuse of the buprenorphine-naloxone product in postmortem cases. Deaths and fatal poisonings due to parenteral buprenorphine-naloxone abuse occurred frequently, and abuse of the combination product was proportionally even more fatal than was abuse of buprenorphine.

The results of this study will assist in medico-legal cause-of-death investigations through providing quantitative reference concentrations for the interpretation of opioid-related deaths. Further, estimating the proportion attributable to prescription opioid abuse compared to that of other opioid use and creating abuser profiles for various opioids can promote public health through proper drug policy. In a clinical context, results may be helpful in evaluating possible drug abuse and compliance among prescription-drug users. Detecting abuse of these important yet addictive medications is vital in promoting welfare and drug safety.

INTRODUCTION

Fatal poisonings occurring annually in Finland number over 1,000, half of which are drug poisonings [1]. The top three drugs causing fatal poisonings in Finland are buprenorphine, tramadol, and codeine. These prescription opioids have, in recent years, taken the front positions away from tricyclic antidepressants and antipsychotics [1]. Antidepressant-related deaths are usually linked to suicides, whereas opioid fatalities involve drug abuse. Drug-abuser deaths typically include a combination of several drugs acting on the central nervous system (CNS). Rather new findings in the death statistics concern the gabapentinoids pregabalin and gabapentin. Along with the increases in their sales and consumption, abuse and deaths related to gabapentinoids seem to be increasing. Undoubtedly the increasing prescription drug abuse with many unintentional fatal poisonings is an undesirable phenomenon.

The aging population with probably increasing pain and demand for medications requires caution to prevent illicit and prescription drug abuse from escalating. Drug abuse causes suffering to drug abusers and their next of kin, and brings disorder in society. Acquisition of drugs may be financed by crime. Related health problems from drug injection, including infections, such as hepatitis B and C and HIV, abscesses, cellulitis, endocarditis, or sepsis, as well as limb amputation and paresis, may require long, expensive hospitalization and lead to disability at work. Opioid maintenance treatment is efficient in treating opioid abusers and diminishing the harm of drug abuse, but diversion and abuse of maintenance medications also occur.

The expanding prescription drug abuse problem is worldwide. The General Assembly of the United Nations has urged its member states to fight against prescription drug abuse, especially through informing the general public and health-care providers [2]. According to the European Union Drugs Strategy, special effort should be taken to reduce drug demand and drug supply [3]. EU member states should invest in information, research, and monitoring of the drug-abuse situation. The key indicators for EU data include drug-related deaths and the prevalence and pattern of problem-drug use in the general population, the topics this thesis aims to cover.

Published postmortem toxicology studies are often based on only a few cases, but medico-legal cause-of-death investigation should not merely rely on case reports [4]. Forensic case reports are useful in discovering new trends, but proper statistical analysis and generalizations require larger, comprehensive data sets. The Finnish postmortem toxicology database provides quantitative data with representative population-based results based on actual laboratory measurements and routine screening of several hundred different drug compounds.

This thesis focuses on exploring laboratory results stored in this extensive postmortem toxicology database, completed with information from cause-of-death investigation issued in referrals and death certificates by forensic pathologists. This thesis aims at developing methods for distinguishing opioid and gabapentinoid poisonings from other deaths related to these drugs, at determining abuser profiles of prescription opioids to provide better understanding of drug abuse for medico-legal casework, and at promoting public health through proper drug policy.

REVIEW OF THE LITERATURE

1 Opioids

1.1 Basic pharmacology

Opioids are psychoactive substances whose pharmacological effects resemble those of morphine or other opiates. Opiates are natural alkaloids of the opium poppy (*Papaver somniferum*), and the term “opioid” refers to opiates, synthetic derivatives of the opium poppy, and endogenous opioid peptides produced naturally in the body, such as endorphins, enkephalins, dynorphins, and endomorphins. Morphine and codeine are opiates, oxycodone and buprenorphine are semisynthetic opioids, and tramadol, fentanyl, and methadone are synthetic opioids. Commonly, the term “opiate” is associated with compounds that test positive in the opiate immunoassay, such as morphine, codeine, heroin, and the heroin metabolite 6-monoacetylmorphine.

Opioids bind to opioid receptors, the main classes of which are μ (mu), κ (kappa), δ (delta), and ORL1 (opioid-receptor-like1) receptors. Opioid receptor μ mediates, among others, analgesia, respiratory depression, euphoria, and physical dependence. Receptor κ mediates analgesia, especially in the spinal cord, and sedation and dysphoria. Receptor δ mediates analgesia, especially in peripheral tissues. The ORL1 receptor is important in pain responses and development of tolerance to μ agonists. Each opioid has a unique binding affinity to opioid receptors, which leads to different profiles of its opioid effects. These effects include analgesia, sedation, euphoria, respiratory depression, miosis, and nausea. In a medicinal context, opioids are useful against pain and cough, and in opioid maintenance treatment (OMT) for opioid-dependent patients.

Table 1 summarizes the pharmacokinetics of opioids and some other drugs. Codeine is a weak opioid against pain and cough. Codeine is mainly metabolized via cytochrome P450 (CYP) 2D6 to its major metabolite morphine.

Tramadol is a weak opioid derivative of codeine. The analgesic effects of tramadol are based on both opioid μ receptor and serotonin and noradrenalin reuptake inhibition. The main active metabolite is *O*-desmethyltramadol (ODT), which is formed by CYP2D6. Tramadol itself has low affinity to opioid receptors, but *O*-desmethyltramadol has significant opioid receptor affinity. Polymorphism of CYP2D6 activity and other CYP2D6-metabolizing medications may influence tramadol’s effects: reduced CYP2D6 activity produces less *O*-desmethyltramadol, which reduces its analgesic effects. Tramadol, as well as other weak opioids, has a ceiling effect: at high dosing, the analgesic effects cease to increase. The concentrations of tramadol and *O*-desmethyltramadol peak at different times in the brain, and a larger dose of tramadol does not lead to a correspondingly increased amount of *O*-desmethyltramadol in the brain [5]. At higher doses, tramadol also lowers seizure threshold by increased serotonin-receptor inhibition [5].

Buprenorphine serves as an analgesic and in OMT. It has a rather complex pharmacology, characterized as a partial μ receptor agonist, a κ and δ receptor

antagonist, and a weak partial agonist of ORL1. In Finland, buprenorphine is usually classified as a medium-strength opioid.

Fentanyl is a potent agonist for receptor μ , 100 times more potent than morphine. Fentanyl can be used as anesthetic or in rapid pain relief by an intravenous route, as well as against chronic pain with transdermal patches. Fentanyl has rapid onset and a short duration of action (Table 1). Its administration route is most commonly transdermal, transmucosal, or intravenous.

Oxycodone is a strong opioid against severe pain, primarily metabolized via CYP3A4 and CYP2D6 to several metabolites, such as the active metabolite oxymorphone and the relatively inactive noroxycodone. Compared to morphine, oxycodone has higher oral bioavailability, faster onset of action, and longer duration of action, but unlike morphine, oxycodone is prone to drug-drug interactions due to its CYP-mediated metabolism [6].

Methadone is used against pain and in OMT, acting as an agonist for receptor μ and an antagonist for receptor NMDA (*N*-methyl-D-aspartate). As medication, methadone is available as a racemic mixture of 50% levomethadone (L-methadone) and 50% dextromethadone (D-methadone). L-methadone acts via the μ -receptor and D-methadone via the NMDA receptor. Via effects on the NMDA receptor, methadone somewhat reduces neuropathic pain and reduces and reverses opioid tolerance. Absorption, bioavailability, clearance, and elimination of methadone show extreme inter-individual variation [7]. The main metabolite, produced via CYP3A4, is pharmacologically inactive EDDP (2-ethylidene-1,5-dimethyl-3,3-diphenylpyrrolidine). Methadone accumulates in tissues, which act as a methadone supply, leading to higher and steadier concentrations in tissues than in blood.

Naloxone is injected to treat acute opioid poisoning, and in sublingual buprenorphine-naloxone combination products, it diminishes intravenous buprenorphine abuse. Naloxone is a semisynthetic opioid, but it is a full receptor μ , κ , and δ antagonist. It has extensive first-pass metabolism, leading to its insignificant effect when administered orally. The full opioid μ and δ receptor-antagonist naltrexone can be administered orally and sometimes serves in treating opioid dependency for highly motivated persons after withdrawal to prevent further opioid use, and in treating alcohol dependence. Orally administered nalmefene is a μ and δ antagonist and a partial κ agonist that has been introduced to reduce alcohol consumption among alcohol-dependent patients [8].

Table 1. The basic pharmacokinetics of the opioids studied, gabapentinoids, and some benzodiazepines [9].

	Oral bio-availability (%)	V _d (l/kg)	Elimination	Main metabolites	Protein binding (%)	T _½ (h)
BPN	sublingual 51 [10]	1.4-6.2	metabolism	NOR (CYP3A4)	96	BPN 2-4 (parenteral), 18-49 (sublingual), NOR 36 (parenteral), 83 (sublingual) [10]
Codeine	59	2.5-3.5	metabolism	morphine (CYP2D6), norcodeine	7-25	1.2-3.9
Morphine	38	2-5	metabolism		35	1.3-6.7
Fentanyl	trans-mucosal 51	3-8	metabolism	norfentanyl	79	3-12
Methadone	85	4-7	metabolism	EDDP, EMDP	87	15-55
Oxycodone	42	1.8-3.7	metabolism	oxymorphone (CYP2D6), noroxycodone (CYP3A4)	45	3-6
Tramadol	68	2.6-2.9	metabolism	ODT, nortramadol	15-20	tramadol 4.3-8.3, ODT 6.3-9.5
Naloxone	2	2.6-2.8	metabolism		46	0.5-1.3
Pregabalin	90 [11]	0.5-0.6	renal excretion		0	5-11
Gabapentin	27-60	0.8-1.3	renal excretion	none	<3	5-9
Alprazolam	88	0.9-1.3	metabolism	α-hydroxy-alprazolam	65-75	6-27
Diazepam	94	0.7-2.6	metabolism	nordazepam, oxazepam, temazepam	96	diazepam 21-37, nordazepam 31-97, oxazepam 4-11
Temazepam		0.8-1.0	metabolism	oxazepam	97	3-13

V_d volume of distribution

T_½ half-life in plasma

1.2 Buprenorphine

Buprenorphine maintenance treatment for opioid addicts has proven successful in many reports, and buprenorphine is now an effective alternative to methadone internationally [12]. Buprenorphine undergoes extensive first-pass metabolism and therefore has low oral bioavailability. Its bioavailability by the sublingual route has been estimated as 51.4% and by the buccal route as 27.8%, although both administration routes involved considerable inter-individual variability [10]. The mean time to maximum plasma concentration following sublingual administration is variable, ranging from 40 minutes to 3.5 hours [13]. Buprenorphine has a large volume of distribution (V_d) and is highly protein bound (96%) [13]. A low correlation ($r^2=0.261$) existed between its mean dose and mean plasma concentration in a study with 17 buprenorphine cases on a maximum daily dose of 8 mg [14]. Buprenorphine is metabolized to an active metabolite norbuprenorphine and the respective glucuronide conjugates [15,16]. Norbuprenorphine has an estimated one-fiftieth the analgesic potency of buprenorphine [17]. The *N*-dealkylation to norbuprenorphine is primarily mediated by CYP3A4 [18]. A considerable variation occurs in reported values of the terminal elimination half-life of buprenorphine, with mean values ranging from 3 to 44 hours [13]. In parenteral administration, its half life is much shorter than by the sublingual route (Table 1). Most of each buprenorphine dose is eliminated as metabolites in the feces, with approximately 10 to 30% excreted in urine [13].

A plateau in buprenorphine opioid effects is consistent with its partial agonist classification, and the fact that nondependent human beings tolerate well single doses of buprenorphine up to 70 times the recommended analgesic dose [19]. A ceiling on the effects of buprenorphine in humans may reduce its abuse liability and improve its safety, and indicate that opioid blockade occurs after acute buprenorphine administration [20]. Buprenorphine appears to have a ceiling for cardiorespiratory and subjective effects and a high safety margin even when taken intravenously [21].

In the pioneering country France, all general practitioners have been permitted to prescribe buprenorphine without special training or licensing since 1995. In France, intravenous diversion of buprenorphine has led to relatively rare overdosing in combination with sedatives, whereas illegal opioid overdose deaths declined substantially [22]. Reports from the United States indicate that the prescription of buprenorphine for opioid-dependence treatment can be incorporated into primary care practice, and many patients, including polysubstance users, thereby benefit [23].

In Finland, buprenorphine has been on the market since 1981, first as a pain medication. As early as 1985-1990, one general practitioner in Helsinki used buprenorphine in the treatment of opioid addicts with questionable results. In 1995, he developed the Benedictus treatment; the regimen included a visit to the doctor, a support person and treatment with buprenorphine [24]. The treatment typically included a benzodiazepine, most often temazepam [24]. The number of patients escalated and finally this doctor lost control and was found guilty of smuggling and selling buprenorphine tablets, and lost his license [25]. This history may have influenced the Finnish drug scene with its frequent intravenous use of

buprenorphine, whereas the supply of heroin is scarce [26,27]. It was not until 2000 that buprenorphine became legal in withdrawal and maintenance treatment of opioid-dependent patients. At first, Finnish opioid addicts mainly obtained their buprenorphine from French general practitioners [28]. Later, restriction of treatment became less strict, and at present, primary health care units are allowed to administer buprenorphine treatment.

Concern about intravenous buprenorphine abuse in Finland arose shortly after those buprenorphine treatments began [28]. The opioid antagonist naloxone has been added to a sublingual formulation of buprenorphine to reduce its intravenous abuse liability. This approach is based on the fact that the sublingual bioavailability of naloxone is only approximately 10% and elimination half-life 1 to 2 hours [29]. A buprenorphine-naloxone combination product (BNX) came into use in New Zealand in 1991, and concern as to its intravenous abuse rose shortly after [30]. In Finland, BNX has been available in OMT since 2004, and since 2008, designated pharmacies can deliver BNX under certain preconditions. Many studies have confirmed the abuse liability of BNX in Finland [31,32] and elsewhere in the world [33-35], but the actual substantial proportion of BNX abuse among fatal buprenorphine poisonings remained unknown until the results of Study VI.

In OMT, many have attempted to prevent intravenous BNX abuse. Crushing soluble buprenorphine tablets does not reduce their clinical effects, but such crushing may reduce their diversion [36]. No studies exist on crushing the sublingual BNX co-formulation. One option for soluble tablets is a soluble BNX film. In reducing diversion and abuse, however, BNX film seems not to be superior to other BNX formulations: diversion and clinical outcomes of the BNX film have been similar to those for BNX tablets [37-39]. In Finland, BNX film use started in summer 2014 in some treatment units with special permission, but thus far, longer Finnish experience with BNX film is still lacking. Crushed BNX tablets and BNX film may be alternatives when OMT medications are taken daily at a clinic, but as take-home doses, these may contribute to abuse as frequently as do other formulations. Electronic medicine dispensers may prevent some OMT patients from diverting their take-home doses, but these had no effect on the availability or price of illegal BNX [40]. Subdermal buprenorphine implants providing low buprenorphine levels for six months have been effective compared to placebo implants [41,42] and were not inferior to sublingual BNX [42], but additional studies on their safety and efficacy are necessary until they are approved for treatment.

2 Gabapentinoids

2.1 Therapeutic use and abuse

Pregabalin and gabapentin are GABA (gamma-aminobutyric acid) analogues which bind to the $\alpha_2\delta$ (alpha-2-delta) subunit of the voltage-dependent calcium channel in the CNS. They have no activity through binding to GABA_A receptors, but in the brain they lead to increased GABA synthesis. GABA is the brain's most important inhibitory neurotransmitter; increases in GABA reduce release of excitative neurotransmitters. Although rather similar medications, pregabalin and gabapentin do exhibit some differences. Unlike that of pregabalin, absorption of gabapentin is saturable, which means that with larger doses some of the gabapentin remains

unabsorbed; the daily dose of gabapentin should be divided into three portions, whereas pregabalin can be administered twice a day [11]. The dose-response relationship of pregabalin is steeper than that of gabapentin [11].

Gabapentinoids are effective in treating chronic neuropathic pain such as postherpetic neuralgia and diabetic neuropathy [43], and pregabalin is also effective against fibromyalgia [43,44]. Pregabalin is somewhat more effective for postherpetic neuralgia and epilepsy [11]. In Europe, pregabalin is approved for generalized anxiety disorder (GAD). In long-term treatment of GAD, pregabalin has been suggested as a first-line drug along with selective serotonin-reuptake inhibitors (SSRIs) and serotonin-noradrenaline-reuptake inhibitors (SNRIs) [45]. Pregabalin has been somewhat effective, as well, in treating restless legs syndrome [46]. It has shown some beneficial effects in alcohol relapse prevention, especially in patients with comorbid conditions such as alcoholism and GAD, but its efficacy for alcohol-withdrawal syndrome remains controversial [47]. Pregabalin use in off-label indications other than fibromyalgia or restless legs syndrome is discouraged due to its lack of effect in clinical studies and its risk of abuse [48]. Although gabapentinoids belong to the group of first-line medications against neuropathic pain, so do some antidepressants and other medications [49], and other options for their various indications are available.

Pregabalin has been on the market in Finland since 2004. Signs of pregabalin abuse emerged in 2007, based on postmortem data, when deaths caused by pregabalin rose from 1 to 7 per annum [50,51]. In 2010, fatal pregabalin poisonings in Finland numbered 15, making pregabalin the eleventh most common cause of fatal poisonings [1]. Pregabalin abusers typically use concomitant benzodiazepines, opioids, and alcohol [50]. The administration route in abuse cases is usually oral, but intravenous abuse also occurs [50]. Although the abuse potential of pregabalin was by then known, the frequency of pregabalin abuse in Finland was unclear until publication of Study IV.

2.2 Concomitant gabapentinoid and opioid use

Both opioids and gabapentinoids are medications against pain, but their indications vary. As pain medications, gabapentinoids are indicated for neuropathic pain, and opioids for nociceptive pain. In severe pain conditions, pregabalin and opioids can be co-administered [49,52-54]. Pregabalin and oxycodone combination therapy against neuropathic pain results in a dose-reduction in both drugs and a superior safety profile compared with that of pregabalin monotherapy [52]. In clinical studies involving diabetic neuropathy and postherpetic neuralgia, gabapentinoid combination therapy with opioids has shown mainly positive responses [53]. Whereas gabapentinoids, among some other drugs, are the first-line medications for various neuropathic pain conditions, strong opioids are recommended as second- or third-line choices because of the potential risk of abuse in long-term use [49]. The European Federation for Neurological Societies recommends, for patients showing only a partial response to these drugs administered alone, a combination therapy of gabapentin combined with opioids or tricyclic antidepressants [49].

Gabapentinoids combined with opioids may also involve abuse. Abuse of pregabalin is increasing, especially among opioid-dependent individuals [55,56]. Abuse of gabapentinoids to get high has recently been reported among patients on both methadone [57] and buprenorphine medication [58]. The substantial proportion

of pregabalin abuse among opioid-related fatalities, however, remained undefined until the results of this thesis study.

3 Benzodiazepines

3.1 Therapeutic use and abuse

Benzodiazepines are psychoactive substances effective for anxiety, insomnia, agitation, muscle spasms, seizures, and alcohol withdrawal, and as premedication for medical procedures. Benzodiazepines bind to the GABA-benzodiazepine receptor complex in the CNS. Their primary target is the GABA_A receptor, a chloride channel activated by GABA. Benzodiazepines reinforce the inhibitory effects of GABA, leading to decreased excitability of neurons and a calming effect on brain functions. Benzodiazepines differ from each other in physiochemical properties such as lipid solubility and rate of absorption and diffusion. Many benzodiazepines involve CYP metabolism, which is a potential pharmacokinetic mechanism resulting in drug-drug interactions with other drugs.

Benzodiazepine findings are especially challenging to interpret because of their common metabolic pathways (Table 1). Diazepam is metabolized to the active metabolites nordazepam and temazepam, which are further metabolized to oxazepam. Temazepam and oxazepam are both also parent drugs produced and sold as such. This makes it difficult to know what product the deceased had taken in the usual situation of scarce background information. Differentiating parent drugs from metabolites is important when studying what product or how many different benzodiazepines a victim has consumed, and when interpreting the concentration results. In the literature, this problem of exactly which compounds have been consumed is usually neglected. Diazepam and oxazepam concentrations, for example, may be given as such and both be regarded as parent drugs, without dividing them into metabolites and parent drugs [59].

Benzodiazepines are the most abused and addictive group of medications in Finland [60]. Some researchers have suggested that they should not be prescribed to anyone drug-addicted because of the abuse risk [61]. Benzodiazepine abuse is usually oral with large doses, but intravenous abuse also occurs [60]. Concomitant use of other drugs among benzodiazepine abusers is highly common.

Because prescribing benzodiazepines always includes the risk for abuse, diversion, and addiction, the Finnish National Supervisory Authority for Welfare and Health (Valvira) has created instructions for prescribing benzodiazepines. These instructions state that benzodiazepine treatment should be short, usually a maximum of 4 to 12 weeks, including the gradual termination of treatment [62]. Besides benzodiazepines, many conditions can and should be treated with other, more suitable and less addictive medications [62]. Most patients prescribed benzodiazepines will not become dependent, but because the number of benzodiazepine users is large, the problem of abuse and dependence is considerable [62]. The Hospital District of Helsinki and Uusimaa (HUS) has also created instructions, ones based on those initiated by Valvira. These instructions point out that short-acting benzodiazepines such as lorazepam, alprazolam, triazolam, and midazolam should be avoided because of the abuse risk. Diazepam 10-mg tablets and temazepam should be avoided because of their desirability among drug abusers.

Prescription of the first benzodiazepine or other potentially addictive medication should depend on careful consideration [62].

Recreational abuse of one benzodiazepine, phenazepam, emerged in 2010 in Europe and the United States [63,64]. Phenazepam is available in Russia for sleeping disorders, epilepsy, and alcohol withdrawal. Although it is not available as a medicinal product in Finland, phenazepam's abuse has been a widespread phenomenon also in Finland [63]. The Finnish Medicines Agency (Fimea) classified phenazepam as a narcotic in Finland in May 2014.

3.2 Concomitant opioid and benzodiazepine use

OMT clients are particularly vulnerable to concomitant opioid and benzodiazepine use and may try to potentiate the effects of opioids with benzodiazepines [65]. Among opioid users, drugs not depressing the CNS, or non-pharmacological treatments should be the preference over benzodiazepines [65]. Opioid-dependent subjects in buprenorphine maintenance treatment who also have benzodiazepine dependency or abuse experience a poorer outcome in life than do patients without problematic benzodiazepine use or patients using no benzodiazepines [66]. Some opioid addicts seem to use benzodiazepines as a self-medication for psychiatric comorbidities or to counter negative affect [67]. Self-medicating with benzodiazepines may appear in OMT with an inadequate dose of OMT medication [68]. Benzodiazepine prescriptions in buprenorphine maintenance treatment are associated with increasing accidental injuries, but not with outcomes of opioid treatment [69].

Although benzodiazepines and opioids are metabolized by CYP enzymes, pharmacokinetic interactions between them seem mostly clinically irrelevant [65,70]. Interactions between benzodiazepines and opioids seem mainly pharmacodynamic and can result in potentiated respiratory and other CNS depression [70].

After publication of Studies **I** and **II**, other studies have also confirmed the frequency of combined opioid and benzodiazepine abuse and its consequences. Benzodiazepines are common findings in opioid-related fatalities [71]. Benzodiazepines have a wide safety margin when consumed alone, without other CNS depressants, which may lead to underestimation of their dangerous nature when combined with opioids [71]. The combination of methadone and benzodiazepines may be more dangerous than the combination of buprenorphine and benzodiazepines, because the former have led to higher hospitalization rates and worse medical outcomes [72]. Among chronic pain patients on long-term opioid treatment, concomitant opioid and benzodiazepine consumption is common, as is illicit drug use and other addictive behaviors [73].

4 Drug poisonings

4.1 Fatal poisonings in Finland

In Finland, fatal poisonings number annually 1,000 to 1,200 (Figure 1). Of all the fatal poisonings, alcohol and drugs each contributes to 40 to 50%; poisonings other than those alcohol- and drug-related mainly result from carbon monoxide. Fatal poisonings have generally declined, but an increase is evident in poisonings related to drug abuse, including both illicit substances and abused prescription medications. In 2010, fatal opioid poisonings numbered 189, being the most important drug group causing fatalities. Opioid poisonings involved buprenorphine, tramadol, codeine, fentanyl, methadone, and oxycodone, and only two cases of heroin. In second place were antidepressants, numbering 106, and in third place, antipsychotics, numbering 64. [1]

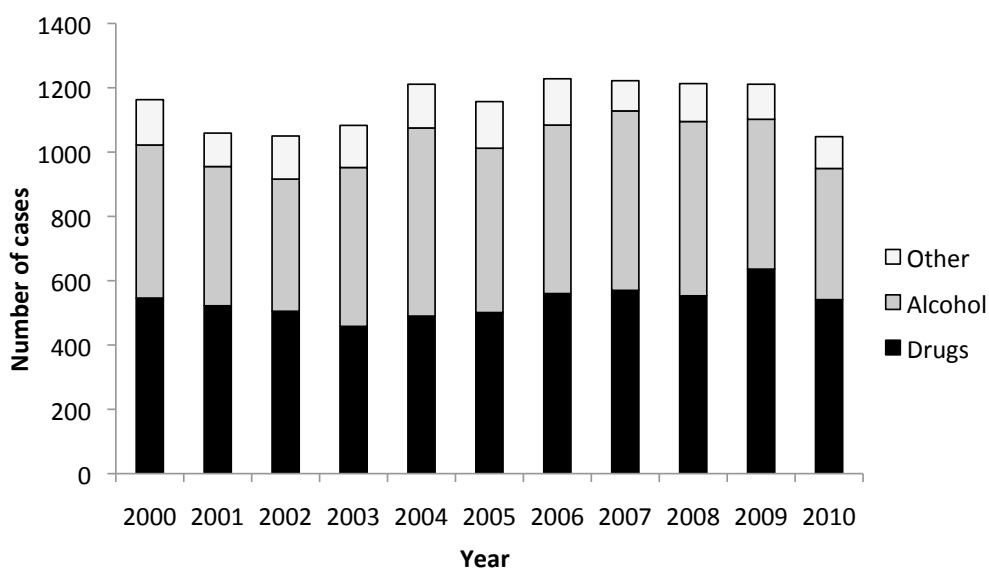


Figure 1. Fatal poisonings in Finland from 2000 to 2010, based on data from Vuori et al. [1,51,74,75].

4.2 Opioid poisonings

Non-fatal opioid overdoses in Finland peaked in the year 2000 and declined rapidly thereafter [76]. Back then, the chief abused opioid was heroin, but buprenorphine has since replaced it, also in non-fatal overdoses [76]. The number of non-fatal buprenorphine poisonings was then lower than was the number of heroin poisonings. Polydrug use more often involved non-fatal buprenorphine overdoses, but severe respiratory depression was rarer among buprenorphine than among heroin overdoses [76].

Opioid poisonings are quite straightforward and easy to treat in hospitals, but the difficulty lies in the fact that potentially fatal opioid poisonings usually occur outside hospitals; most often the deceased are found dead. Opioid poisonings in this study refer to deaths occurring after opioid overdose, as overdose is, among opioid dependents, their most common cause of death [77,78]. A classic pattern of an opioid poisoning involves a long-time drug abuser: an opioid-addicted man in his thirties, who is found dead outside a hospital with a syringe and empty packages of opioids and other medications [79-85]. Injecting as the primary route of administration increases the risk of premature death [77,79]. Polydrug toxicity is the major factor causing opioid poisonings, whereas drug impurities or variations in illicit drug purity are practically insignificant [84,85].

The main mechanism of fatal opioid poisoning is respiratory depression. Tolerance to respiratory depression is relatively slow and incomplete compared to tolerance to the euphoric effects of opioids [86]. Risk for overdose is greater after abstinence, because the dose previously necessary for euphoric effects can cause respiratory depression due to diminished tolerance. Benzodiazepines and alcohol are dangerous when used concomitantly with opioids, because they all inhibit CNS via acting on the GABA_A receptor. In these polydrug cases, naloxone may be insufficient, because naloxone inverts only that respiratory depression due to the opioid, without affecting the consequences of other compounds [86]. According to studies with forensic case series, a typical mechanism of death in opioid poisoning is prolonged asphyxia including cyanosis, pulmonary edema, and multivisceral congestion [79,80,87,88].

5 Postmortem toxicology data

5.1 Postmortem studies

Postmortem toxicology data are based on measured drug concentrations in autopsied bodies. Analyses provide information on multiple drug findings and new trends in drug abuse. In postmortem toxicology, no prior information on drugs taken is necessary because broad-spectrum drug screening methods are generally applied. Postmortem blood concentrations, usually measured in whole blood, may, however, differ from therapeutic reference drug concentrations measured in living persons. A therapeutic reference concentration is for many drugs measured for plasma, although some medications, such as cyclosporin and tacrolimus, are redistributed into the erythrocytes, and their concentrations are measured in whole blood even among living patients. For opioids, the postmortem blood/therapeutic plasma concentration ratio is 1, suggesting that in a comprehensive postmortem data set, median postmortem concentration is within the established therapeutic range for plasma

[89]. For gabapentin, this ratio was 1.8, and for pregabalin, 1.6, suggesting that median postmortem concentrations of gabapentinoids are above the therapeutic range divided by the upper limit of the therapeutic range; this is likely due to postmortem redistribution of drugs (PMR) [89]. This suggests that postmortem concentrations of gabapentinoids might be somewhat higher than they are antemortem.

Published postmortem toxicology database studies typically include only cases in which an opioid or another substance was the cause of death or at least a contributory factor on a death certificate [90,91]. Especially if the studies are based on general registers, not all drugs are taken into account, and the studies may underestimate the total number of drug findings. In polydrug poisonings, the individual substance that is the most important cause of death may remain unclear. In Finnish postmortem data, when compared to the whole population, drug abusers are overrepresented. Consequently, postmortem results provide good estimates, especially for young abusers [92].

5.2 Postmortem drug concentrations

Postmortem blood drug concentrations should be measured in femoral venous blood because of PMR. Due to PMR, postmortem concentrations among tissues vary. Reasons for this include differences in postmortem drug release from different organs, such as the gastrointestinal tract, lungs, myocardium, and liver, from putrefaction, blood movement, coagulation, hypostasis, and drugs' pharmacokinetic and chemical properties, such as acidity, lipophilicity, binding to proteins, high V_d , or residual metabolic activity [93]. PMR is relevant especially for drugs with a high V_d [94]. V_d is the theoretical volume which defines the distribution of a medication between plasma and the rest of the body. The higher the V_d , the more of the drug will be distributed in the tissues than in plasma. Among opioids, methadone has the greatest V_d (Table 1), indicating more accumulation in the body. When the distribution is not uniform, after death the distribution will possibly become more uniform because of stabilization of the concentration gradient [94].

Peripheral samples from femoral blood are the least subject to PMR and should generally be the choice for concentration measurements [93,95,96]. Some PMR occurs also in femoral blood. Some evidence suggests that postmortem concentrations of morphine and codeine [97], and of fentanyl [98], especially in fentanyl-abuse cases [96,99], may be higher than their respective antemortem concentrations. These small differences are, however, probably insignificant in the interpretation of toxicological findings in death cases. For example, median peripheral blood concentrations for codeine at mortuary admission was 0.108 mg/l, and at autopsy, 0.114 mg/l [100]. These figures were, respectively, for methadone 0.377 and 0.448 mg/l, for morphine 0.262 and 0.253 mg/l, for oxycodone 0.141 and 0.142 mg/l, and for tramadol 1.531 and 1.045 mg/l [100]. The difference was statistically significant only for methadone [100], but both of the methadone median concentrations were well within therapeutic range.

In blood circulation, drugs are dissolved in plasma, bound to plasma proteins or bound to membranes, or contained in the erythrocyte cytoplasm [93]. Plasma proteins can act as a reservoir of any circulating, inactive drug. After death, blood proteins such as albumin leak out of the bloodstream into tissues, leading to reduced

concentration of albumin-bound drugs in the blood [94]. High postmortem drug concentrations can sometimes result from transfer across previously impermeable body barriers, such as resulting from absorption through the gastrointestinal tract, lungs, liver, myocardium, or urinary bladder [93,94]. Blood drug concentrations may then be higher near organs in which that drug is normally concentrated, and drug concentrations measured in blood may depend on the sample site [94]. This may be important in traumas that damage internal organs, especially organs near femoral veins, from which blood samples usually are collected. The time-interval between death and sample collection may affect postmortem drug concentrations. The opioids and gabapentinoids studied here are, however, rather stable in plasma and urine [9]. During body putrefaction, bacteria and microorganisms can synthesize ethanol and metabolize certain drugs such as benzodiazepines [93].

Drug concentrations may become higher or lower than expected due to drug-drug interactions such as inhibition or induction of drug metabolism. Opioid metabolism involves, for example, several CYP isoforms. Codeine is a substrate for CYP2D6, an enzyme whose activity is extremely variable due to genetic polymorphisms. The ultrarapid-metabolizer phenotype of CYP2D6, due to gene duplication, can lead to high morphine concentrations after only a low dose of codeine, whereas poor metabolizers lacking CYP2D6 activity produce virtually no morphine [101,102]. Tramadol's analgesic effects, side-effects and risk for poisoning increase among ultrarapid CYP2D6 metabolizers due to increased *O*-desmethytramadol formation [103]. The clinical significance of genetic CYP2D6 polymorphism in the analgesic effect of oxycodone is controversial, although the active metabolite oxymorphone is produced by CYP2D6 [6]. Because oxycodone is mainly metabolized by CYP3A4, inhibition of CYP3A4 leads to increased exposure to oxycodone [6]. High postmortem methadone concentrations occur in slow metabolizers of CYP2B6 [104]. Even those with normal CYP activity may become temporarily poor metabolizers when taking concomitantly CYP-inhibiting medications, such as when a codeine user takes the concomitant CYP2D6-inhibitors fluoxetine, paroxetine, or terbinafin. Unlike for opioids, metabolism of the renally-excreted pregabalin and gabapentin in humans is negligible, but pharmacodynamic CNS depression by other drugs can lead to increased gabapentinoid toxicity [11].

When opioids are administered regularly, tolerance increases. Tolerance may be one reason for overlapping antemortem concentrations among regular drug users, such as drugged drivers, and postmortem concentrations [105,106]. In non-fatal pregabalin poisonings, as well, concentrations may be considerably higher than the drug's therapeutic ranges [107,108]. Loss of tolerance may play a significant role in the deaths of those drug abusers who have undergone some period of abstinence, such as after their release from prison or shortly after detoxification treatment [84].

In parenteral administration, such as intravenous injections or intranasal snorting, drug doses may be lower than when administered orally, because, for many opioids, intravenous administration leads to a rapid onset of action and full bioavailability. Consequently, postmortem concentrations of intravenously abused drugs may be within therapeutic ranges even in fatal drug poisonings [81,82]. Those dead from opioids usually show signs of prolonged asphyxia, and particularly buprenorphine poisonings may be delayed: the deceased dies of prolonged respiratory depression while asleep [81,87]. Then the postmortem concentrations will be lower than are drug peak concentrations after drug administration. Drug concentrations alone can

rarely determine the manner of death; case histories should always receive close scrutiny [94,98].

6 Toxicological drug screening

In postmortem toxicology, drug screening aims to reveal all the relevant drugs the deceased had used recently. In blood, drugs are mainly present as the parent compounds, except for prodrugs, which are present as active metabolites. Urine samples include drug metabolites. The time-scale for drug detection depends on the specimen screened. Blood concentrations reveal the influence of drugs at the time of death. Urine concentrations reveal drug use after a longer period, usually within a few days following drug consumption, even when the clinical drug effects have already vanished. Other possible matrices in postmortem toxicology include, for example, vitreous humor, hair, muscle, liver, fat, lung, bone, and even the larvae found in putrefying bodies [109]. These matrices are primarily utilized in qualitative drug analyses to reveal drugs the deceased had consumed, or their metabolites. Factors affecting drug concentrations and findings in postmortem data mostly involve PMR, putrefied samples, contamination with tissue fluids, and drug decomposition [94,109].

Among living patients, drug screening provides information on patient compliance. Blood, serum, or plasma samples provide information on dosing and poisonings. Methadone metabolism has great inter-individual variability, and measuring methadone serum concentrations of OMT patients helps in adjusting for the proper dose. In suspected poisonings, drug concentrations measured in blood samples allow specific diagnostics and treatment. Urine is a useful screening matrix in revealing inappropriate substance use, such as illegal drug use in OMT. Other possible screening matrices in the clinical setting include oral fluid, hair, and sweat [110]. In routine urine screening among living patients, the first test is traditionally a qualitative immunoassay-based test indicating a substance's presence or absence. Prevalence of both false positives and false negatives in these immunoassay-based screening tests is rather high, and the results need confirmation by reliable mass-spectrometry-based methods, at least in cases where sanctions or judicial consequences may follow a drug-positive test result. In research and compliance monitoring, developing and applying sufficiently accurate laboratory methods for drug screening is vital. Prior to the results of Study V, as tested among BNX maintenance patients, typical urine naloxone concentrations after sublingual administration of BNX were unclear.

Urinary parent/metabolite ratios may be helpful in monitoring compliance, because patients may try to adulterate their samples. Urine-sample adulteration may include, for example, dilution, substitution, or addition of substances to the sample. A drug-abusing patient in methadone maintenance treatment may, for example, add liquid methadone to a urine sample bought from someone using no medications, in order to produce a sample demonstrating only the prescribed methadone. In routine immunoassay-based presence- or absence-screening, this adulteration may be impossible to detect, but quantitative confirmation analysis can prove adulteration. EDDP can serve as a marker of compliance among patients in long-term methadone treatment: a high concentration of methadone combined with no EDDP suggests sample adulteration [111]. Another approach in compliance monitoring can be

quantitative measuring of the urine EDDP/creatinine ratio, which may predict the dose of methadone consumed [112].

7 Substance abuse

7.1 Definition of drug abuse

Drug misuse typically refers to substance use not appropriate for medical indications or not matching prescribed dosing [113]. Drug misuse involves, for example, too-large or too-small dosing, and it may be wilful or unintentional. Drug abuse means that the substance is used for nontherapeutic purposes, usually to obtain psychotropic effects such as euphoria, sedation, or to cause anxiolytic effects [113]. Some definitions of drug abuse also include contradiction of medical advice, taking medication against prescription, drug use causing harm to the user, or illegal substance use [113]. In the present work, drug abuse means, consistently with these definitions, intentional recreational substance use as narcotics.

7.2 Methodological approaches

Different approaches are available for studying substance abuse and its properties and prevalence. Animal studies help us to discover drug properties and toxicity [114,115] as well as some abuse potential [116]. Case reports usually give the first insights into possible abuse problems [117], to be followed by longer case series reports [80-83]. Traditional surveys concerning drug abuse include questionnaires and population surveys [118-120], or surveys in addiction clinics [121], or needle-exchange programs [32]. Adverse drug reaction and pharmacovigilance database surveys may provide indications of drug dependency or addiction [122]. Calls to poison centers provide information on trends in emerging drug toxicity, overdoses, and abuse [123]. Seizures by Customs reveal trends in drug supply and new recreational substances [124]. Studies on apprehended drivers provide information on the range of medications used and abused as well as their concentrations related to psychomotor performance [63,105,106,125]. Finally, therapeutic drug monitoring produces data on the clinically relevant drug concentrations of certain drugs in plasma, serum, or whole blood.

Substance abusers participate poorly in population-based studies such as questionnaires or interviews, and they may underreport their drug use. It is also possible that the substances they take may have remained unknown even to themselves. Another type of study has been conducted to overcome the problem of scarce participation. Patterns of drug abuse in local communities have been monitored by wastewater analysis, which means detecting drugs and metabolites in communal sewage water [126,127]. Social media has nowadays a profound impact on public health, and studies of Twitter comments have provided real-time epidemiology of the drug-abuse scene [128,129]. Anecdotal internet reports have provided information on relatively new psychoactive substances and their abuse potential. An increase in the online drug debate typically precedes clinical drug abuse events at population level [130,131]. Computer models have predicted what types of individuals become opioid abusers or dependent on opioids. Those more likely to develop opioid abuse or dependency are, for example, male, younger, prescribed more concomitant medications, and with more psychiatric disorders and a

prescription history of more opioids in larger amounts; they also use more medical services [132]. Studies on genetics may provide better understanding of drug addiction. Copy number variations in the human genome may contribute to susceptibility or resistance to opioid dependency [133].

7.3 Drug abuse in Finland

The lifetime prevalence of any illicit drug use among Finns in 2010 was, according to population surveys, 17%, and the most common illegal drug was cannabis (Table 2). Lifetime prevalence of non-medical prescription-drug use in 2010 was 7%, and of these drug abusers, 44% had also tried illicit drugs [118]. The prevalence of problem users of opioids has been estimated as based on Finnish health care registers. This register data come from various hospital discharge registers, the national police information system, the register of those caught driving under the influence of drugs, and from the national infectious diseases register, hepatitis C cases. In 2005, problem opioid users numbered 3,700 to 4,900, or 0.13 to 0.18% of the Finnish population [134]. In 2012, problem opioid users numbered 12,700 to 15,100, rising to 0.38 to 0.45% [135]. Based on these figures, drug abuse in Finland has clearly increased.

Buprenorphine has been the most commonly abused opioid in Finland since the first years of the 21st century [136]. Reasons for its abuse include treatment of addiction or withdrawal symptoms, as well as recreational use and euphoria seeking. Self-treating is common among regular intravenous drug users, of whom 78% reported their reason for buprenorphine abuse to be self-treatment; only 10% had a recreational purpose [32].

Polydrug abuse enhances the positive effects of other drugs, such as euphoria [137]. Lintonen et al. forecast that by the year 2020, misuse of medicinal drugs and synthetic designer drugs, and the growing of cannabis at home will increase markedly [138]. Increasing abuse of medicinal drugs will lead to an increasing number of drug-related deaths [138]. Population aging will not reduce drug abuse, but the Finnish drug-abuser population seems to become older [138]. This phenomenon leads to increased need for health care services and OMT, which usually is a long-lasting therapy taking years or even the rest of one's life.

Table 2. Lifetime prevalences (%) of illicit drug use among Finns aged 15 to 69 according to population survey data from Metso et al. [119].

	2002	2006	2010
Any illegal drug	12	14	17
Cannabis	12	13	17
Amphetamine	2	2	2
Heroin or morphine	1		
Heroin		0	0
Buprenorphine or other opioids ^a		1	
Buprenorphine			1
Other opioids ^a			1
Sedatives, anxiolytics, analgesics	7	7	6

^a tramadol, fentanyl, codeine, oxycodone, morphine

Finnish drug users have typically been rather young, but this situation may be changing. In 2007, fatal intoxications among drug addicts had the highest frequency in the age group 25 to 29 years, but in 2012, in the group 30 to 34 [139]. Typical for Finnish drug abusers is mixed use of medicinal opioids, alcohol, and benzodiazepines [118,120,121,137,140,141]. Intravenous buprenorphine abuse is particularly common among young people [121]. Mixed drug and alcohol consumption is responsible for the majority of drug-related deaths in Finland. Piispa et al. divided fatal drug use into three groups: compulsive and addictive drug use, uncontrolled mixed abuse of various substances, and self-medication of mental and physical disorders [140]. Concomitant and risky alcohol- and various-medication consumption frequently occur, especially among young people. Mental and somatic health problems and various social problems are common among drug abusers and in drug-related deaths [118,140].

When compared to other Nordic countries, Finland's drug-abuse profile widely differs [27,139]. In 2007, the most common cause of death in fatal poisoning in Finland was buprenorphine, in Denmark methadone, and in Norway and Sweden heroin [27]. In 2012, heroin maintained its position in Norway, but methadone led among Swedish opioid poisonings, and buprenorphine and other prescription opioids have become more frequent findings in opioid deaths also in Sweden and Norway [139].

7.4 Other prescription drugs with abuse potential

Opioids with their stronger euphoric effects may serve as the most desired and addictive drugs-of-abuse. Apart from benzodiazepines, the Z-drugs (zopiclone, zolpidem, zaleplone) and gabapentinoids, many other possible alternatives to prescription drug abuse exist. ADHD medications such as methylphenidate [122] are amphetamine-like stimulants. High-dose use of the cough syrup dextromethorphan may induce dissociative hallucinations or mild euphoric effects [142]. The antidepressant bupropion may produce stimulating, amphetamine- or cocaine-like effects at high doses [117,143]. Anesthetic ketamine use may lead to out-of-body experiences, alteration of one's sense of time, hallucinations, and dissociative as well as sedative effects [144]. With subanesthetic doses, the anesthetic propofol may produce euphoria, disinhibition, and sedation [145]. Antipsychotic quetiapine abuse may mostly derive from its easy availability for polysubstance-dependent individuals [146], although it also has the anxiolytic, calming, and sedative properties that drug-abusers seek [147]. A muscle-relaxant, carisoprodol, which metabolizes to the anxiolytic meprobamat, has substantial abuse potential, and The European Medicines Agency has recommended its being removed from the market in Europe [148]. Data on other muscle-relaxant abuse are scarce, but drug abusers seem to abuse the muscle-relaxant tizanidine, possibly because of its sedative effects. Sedative properties also appear in older-generation antihistamines.

8 Opioid maintenance treatment

8.1 Need for treatment

According to ICD-10, the diagnostic criteria of opioid dependence include craving for opioids, difficulties in controlling opioid use, physiological withdrawal, increased tolerance, higher priority assigned to opioids than to other interests, and persistent opioid use despite its harmful consequences [149]. Means of treating opioid dependence include agonist therapy with buprenorphine or methadone, withdrawal therapy with lofexidin, clonidine, or other medications, antagonist therapy with naltrexone, and psychosocial therapy [150]. Naltrexone antagonist therapy is suitable only for those highly motivated, in order to prevent relapses, usually after the acute withdrawal treatment. Psychosocial therapy improves results when combined with medications, but is only rarely the choice, due to its immediate costs. Treatment for other drug dependencies, such as dependence upon hallucinogens, stimulants, cannabis, or amphetamines, involve mainly symptomatic treatment. [150]

OMT has proven efficient in diminishing opioid-related mortality [77,84,85,151]. In 2009, the number of patients in OMT in Finland was estimated at approximately 1,800 [152]. In November 2011, this number was 2,439 [152]. In 2012, problem opioid users, including patients in OMT, numbered 12,700 to 15,100 [135]. Based on these numbers, Ollgren et al. conclude that only 20% of the problem opioid users in Finland receive OMT, whereas on a European scale, the estimated percentage is over 50% [135,151].

8.2 Treatment organization

According to the Finnish Act on Welfare for Substance Abusers (41/1986), a municipality should organize appropriate treatment for substance abusers [153]. OMT is administered according to the Decree of the Ministry of Social Affairs and Health on the detoxification and substitution treatment of opioid addicts with certain medicinal products (33/2008) [154]. Inclusion criteria for OMT necessarily include opioid dependency (according to the ICD-10) and a failed attempt at opioid withdrawal treatment [150]. The patient must have a treatment plan with medications and know the goal of the treatment, other medicinal and psychosocial treatment, rehabilitation, and follow-up of the treatment [150]. A proper therapeutic relationship involving doctor and patient is a key factor, but laboratory methods may also be applicable in screening and monitoring drug abusers [150].

Withdrawal treatment (2% of the OMT patients in 2011) aims to stop all use of narcotics, including OMT medications [152]. Rehabilitative substitution treatment (73%) aims at rehabilitation and coming off narcotics [152]. Harm-reducing substitution treatment (24%) aims at improving the quality of life and reducing drug-related harm, such as illegal opioid use, injection, infection, and crime [152].

OMT can be given in specialized addiction treatment units (66% of the Finnish patients in 2011), health care centers (21%), specialized health care (11%), or in prisons (2%) [152]. OMT medications are delivered from the units daily, but patients well committed to the program may receive home medications for 1 to 7 days at a time, sometimes 15 days. Need for proper control of drug abuse remains, because OMT medications also have abuse potential. To prevent intravenous

methadone abuse, for example, methadone distributed from the OMT centers is diluted with juice.

Patients have the possibility of receiving their BNX medication at a designated pharmacy on the basis of the so-called pharmacy agreement, and in 2011, 7% of the patients in rehabilitative substitution treatment received their medications from such a designated pharmacy [152]. These patients need regular contact with their treatment unit, because they may have relapses in drug abstinence. The first experiences of BNX dispensing in designated Finnish pharmacies have been considered positive, with only 26% of the pharmacies reported any relevant problems [155]. OMT medications are free for patients attending treatment units, but the patients must pay for the medications themselves when received from their designated pharmacies.

8.3 OMT medications

The choice between buprenorphine and methadone should be based on individual considerations [150]. According to the latest Cochrane review, buprenorphine and methadone suppressed opioid use equally, but methadone seemed to be superior to buprenorphine in retaining patients in treatment when used with flexible doses adjusted to patient need [12]. With fixed medium or high doses, no differences between buprenorphine and methadone were detectable [12].

According to WHO, buprenorphine products should generally be used in weaker and methadone in stronger opioid addiction, but those who inject buprenorphine should primarily be treated with methadone. Buprenorphine maintenance treatment appears to be, however, an effective treatment also for opioid dependents using mainly buprenorphine intravenously [156]. Choosing between methadone and buprenorphine is not straightforward. On the one hand, if buprenorphine has been the main drug causing opioid dependency, one could argue why treat drug addicts with that same opioid. On the other hand, giving the stronger full opioid-receptor agonist methadone to treat dependency upon a weaker opioid might seem controversial. In Finland, opioid dependence has been mainly associated with intravenous buprenorphine abuse since the early 2000's, but use of BNX in OMT is high. In 2011, 58% of the patients in OMT received buprenorphine-naloxone, 38% methadone, and 4% buprenorphine [152].

The European Medicines Agency's Pharmacovigilance Risk Assessment Committee recommended in July 2014 suspension of the commercial oral methadone solution available in Finland, Norway, and Sweden, because it contains the additive high-molecular-weight povidone [157]. Based on adverse events in Norway, this povidone accumulates in cells of vital organs when abused intravenously [157]. In Finland, a commercial methadone solution with this type of povidone as an additive is currently used in many OMT clinics with special permission, until a new formulation becomes available.

9 Prescription drug consumption and abuse

Since the beginning of the 21st century, prescription opioid consumption and opioid-related deaths have increased worldwide [151,158]. More specifically, fatal and non-fatal heroin poisonings have decreased, while mortality due to prescription opioids has increased [159]. Reasons for prescription opioid abuse include safety misconceptions, drug purity, easy transportation, and easy availability. More opioid prescription and consumption may lead to increasing abuse rates. In the United States, urine drug-screening among chronic-pain patients on opioid medications revealed that 75% of the patients took their medications contrary to the prescription [160].

Registered prescription opioid sales have increased in Finland in DDD (defined daily doses)/1,000 inhabitants/day from 10 in 2000 to 16.5 in 2011 (Table 3). Sales of codeine have almost doubled, but sales of tramadol have increased by only less than a third. Sales of buprenorphine and methadone for OMT have increased, as have the numbers of patients under treatment, but sales of buprenorphine as an analgesic have also increased markedly. Although these increases in prescription opioid consumption and abuse seem evident, the differing abuser profiles of prescription opioids on a national scale have been unclear until the results of Studies III and IV.

The struggle against increasing prescription opioid abuse has inspired development of abuse-deterrent formulations to prevent parenteral opioid abuse. These include, for example, tablets physically resistant to crushing and dissolving, agonist-antagonist combination products, and products incorporated with aversive ingredients when administered by the nasal route [165]. Although these abuse-deterrent formulations reduce the abuse potential of these drugs, they may shift opioid consumption further towards other prescription-opioid formulations or even towards illegal opioids [166]. After publication of the original articles in this thesis study, heroin deaths have, indeed, increased in certain areas. In North Carolina in the United States, heroin overdose deaths have increased markedly: in January 2007, for each heroin death, 16 prescription opioid deaths occurred, but in December 2013, only three [167]. In that state, a transition to heroin had, however, already begun, prior to their introduction of tamper-resistant prescription opioids [167]. In Florida during 2011-2012, heroin-caused mortality increased, while benzodiazepine- and opioid-related deaths decreased, possibly due to a stronger regulation policy for prescription medications [168].

Real-time electronic prescription databases in some jurisdictions in the United States prevent prescription drug abuse [169]. In Finland, as well, electronic prescriptions should reduce drug abuse. A patient can, in general, prohibit prescription inquiries from doctors other than the one who prescribed the medication, but the prescribing doctor is allowed to see all prescription data on narcotic medications and medications mainly acting on the CNS [170]. A patient is allowed to receive prescriptions on paper upon request until the first of January 2017, unless the prescription is for mainly CNS-acting or narcotic medications. All prescriptions for the latter should be electronic from the beginning of 2015. Only

small private practices handling fewer than 5,000 prescriptions per year may still use prescriptions on paper until the first of January 2017. [170]

Customs play a significant role in preventing illegal importation of addictive drugs. If such drugs pass Customs, the police attempt to stop their distribution. In Sweden, only 20% of those who died of buprenorphine or methadone poisoning had a filled prescription for these drugs, suggesting that the majority of abusers purchased their drugs from illegal sources [171]. Today's societies are confronting a struggle between a need to diminish illegal use and to support patients needing efficient pain- and OMT medication.

Table 3. Opioid and gabapentinoid sales in Finland, data from Finnish Statistics on Medicines 2000-2012 [161-164].

	DDD (mg)	DDD/1,000 inhabitants/day				Products
		2000	2004	2008	2011	
Buprenorphine, analgesic	1.2	0.11	0.13	0.17	0.56	Soluble tablet, transdermal patch, injection
Buprenorphine, OMT	8	0.07	0.07	-	-	Soluble tablet
Buprenorphine, OMT, combinations	8	-	-	0.29	0.48	Soluble tablet (with naloxone)
Codeine, combinations		5.22	8.50	9.86	10.11	Tablet (with paracetamol or ibuprofen), oral solution (cough syrup)
Fentanyl	1.2/0.6 ^a	-	0.92	1.47	1.19	Soluble tablet, injection, soluble film, transdermal patch, nasal spray
Methadone, OMT	25	0.02	0.05	0.06	0.14	Oral solution
Morphine	100/30 ^b	0.29	0.23	0.23	0.27	Prolonged-release tablet, oral solution, injection
Oxycodone	75/30 ^c	0.82	0.89	1.25	1.32	Injection, oral solution, prolonged-release tablet, capsule
Oxycodone, combinations	75	-	-	-	0.08	Prolonged-release tablet (with naloxone)
Tramadol	300	2.22	2.77	2.96	2.99	Injection, prolonged-release tablet, capsule, suppository
Pregabalin	300	-	-	3.39	4.74	Capsule
Gabapentin	1800	0.31	1.14	0.96	1.04	Capsule, tablet

^a 1.2 mg in transdermal patches, 0.6 mg in soluble tablet

^b 100 mg in prolonged-release tablets, 30 mg for injection

^c 75 mg in capsules, prolonged-release tablets, or oral solution, 30 mg for injection

AIMS OF THE STUDY

The objectives of this thesis were to determine

- the typical features and laboratory findings characterizing fatal opioid and gabapentinoid poisonings and other opioid- and gabapentinoid-related deaths (**I–IV**)
- means of interpreting postmortem opioid and gabapentinoid concentrations in suspected fatal drug poisonings and means to utilize this drug concentration data in cause-of-death investigation (**I–IV**)
- abuser profiles of prescription opioids (**I–III**) and gabapentinoids (**IV**)
- the urinary naloxone concentration able to differentiate parenteral buprenorphine-naloxone (BNX) abuse from other buprenorphine use (**V**), and, based on this, the proportion of parenteral BNX abuse-associated deaths among all buprenorphine-related deaths (**VI**)
- means to utilize postmortem data and toxicological laboratory analyses in public health and clinical medicine (**I–VI**).

MATERIALS AND METHODS

1 Postmortem cases

1.1 Medico-legal autopsy data

An unexpected death in Finland leads to a medico-legal cause-of-death investigation. Such cases that are known or are suspected to be attributable to accident, crime, suicide, poisoning, occupational disease, medical procedure, or war should always undergo medico-legal examination. The police determine the need for medico-legal death investigation; no permission is required from the bereaved. Of the approximately 50,000 deaths in Finland annually, a medico-legal investigation occurs in about one-fifth. This investigation includes autopsy with additional investigations, often including toxicological analysis, which should always be performed in suspected poisonings, suicides, traffic accidents, and in cases with no specific cause of death. Samples from over 6,000 of those deceased annually undergo toxicological analysis. The Toxicology Laboratory of the Department of Forensic Medicine, University of Helsinki, performs all forensic toxicology in Finland. This laboratory has been since 1997 an accredited laboratory by the Finnish Centre for Metrology and Accreditation (FINAS).

Toxicological samples were taken during the autopsy. The blood and urine samples for quantitative analyses contained 1% sodium fluoride to prevent microbial alteration, and the blood samples came from femoral venous blood. When toxicological samples arrived at the laboratory, they remained stored at +4 °C until analysis was completed, after which they were stored at -20 °C.

The postmortem toxicology database included a forensic pathologist's referral, laboratory analysis results, and information extracted from the final death certificate. The referral included a brief description of the circumstances of death, preliminary laboratory analysis requests, macroscopic autopsy findings, information on the drugs the deceased probably had used, and age and gender. Laboratory data included the drug-analysis results and analysis of other substances found in the specimens. The final death certificate included the cause of death according to ICD-10, and the manner of death according to WHO. A forensic pathologist determines the manner of death according to all autopsy and toxicological data, and background information. Accident as the manner of death may contribute to both unintentional drug overdose or trauma.

According to Finnish legislation, medical record use without personal identifiers is allowed for medical and health research with permission from the institute, without special ethics-committee approval.

1.2 Postmortem studies

The primary postmortem data covered all forensic toxicology cases registered in Finland during 2000 to 2008 and 2010 to 2011 (Figure 2). Studies **I** and **II** included 1,363 opioid-positive cases of those deceased aged 14 to 44. The age limit was set in order to exclude all those other than abusers. Drug abuse among Finnish drug abusers during 1997 and 2008 was concentrated in the age group 15 to 44, with drug

abusers above 45 representing only 2% of all drug abusers [141]. In other studies (III-IV,VI), all cases underwent thorough individual examination to classify the abuse- and other-use cases. The case numbers of Studies III, IV, and VI were, respectively, 2,088, 359, and 225. Criteria to define abuser cases were one or several findings among the following: known history of drug abuse or addiction, known recent parenteral drug self-administration or signs of it, such as new injection marks or injection equipment located near the deceased, and laboratory analysis results of illicit substances such as amphetamine, cannabis, or designer drugs. The other-use cases refer both to medical use and non-medical misuse, such as drug-induced suicides, without evidence of use of the drugs as narcotics.

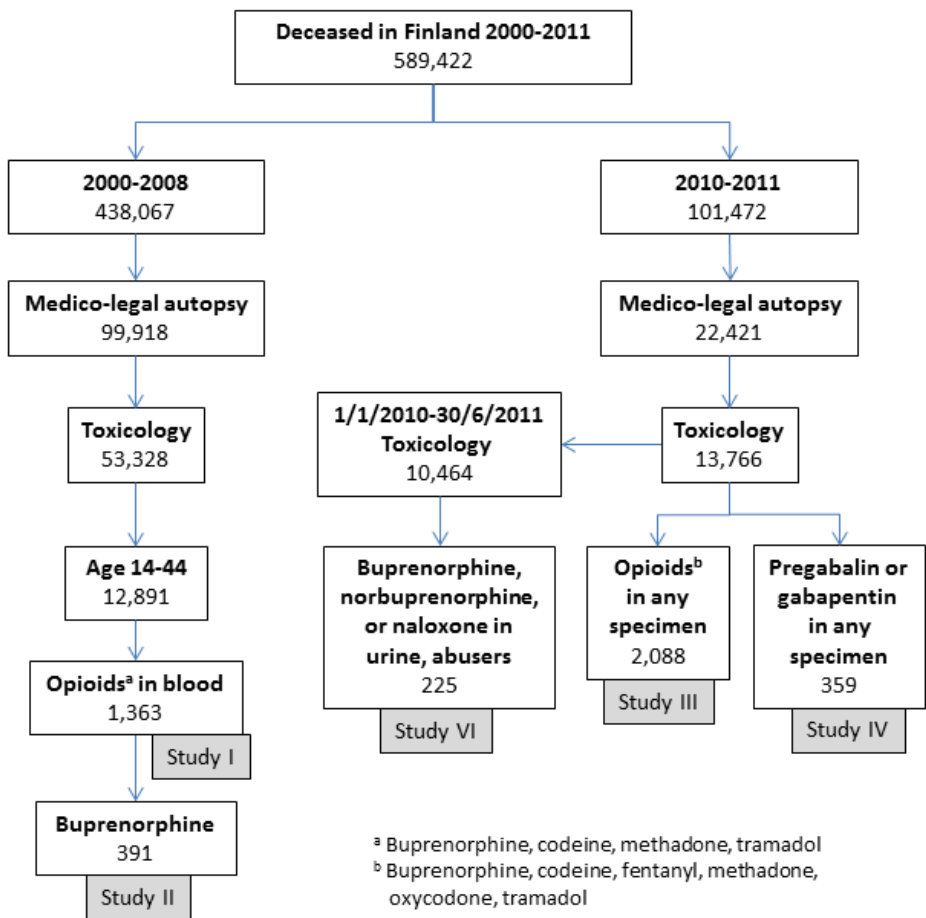


Figure 2. Study populations for the postmortem studies (I-IV,VI).

2 Urine samples from living patients

Study V utilized 40 consecutively collected urine samples from 32 living opioid-dependent patients at three different phases of the OMT in the Department of Psychiatry, Helsinki University Central Hospital. The urine samples were collected under supervision. The Toxicology Laboratory of the Department of Forensic Medicine performed the opioid analysis similarly to its analyses of postmortem samples. The Institutional Review Board of the Department of Psychiatry, Helsinki University Central Hospital, approved the protocol of Study V.

3 Laboratory methods

Toxicological analysis followed a comprehensive multi-technique approach. Urine drug-screening was by a liquid chromatography time-of-flight mass spectrometry (LC-TOFMS) method for approximately 700 drugs [172,173]. Quantitative blood-sample screening for 200 drugs comprised gas chromatography with nitrogen phosphorus detection (GC-NPD) for acidic or neutral drugs [174], GC with electron capture detection (GC-ECD) for benzodiazepines [175], and GC-NPD for basic drugs [176]. Opioid analysis consisted of liquid-chromatography-tandem mass spectrometry (LC-MS/MS) [177]. Quantitative confirmation analyses for both urine and blood were carried out by GC-MS and LC-MS/MS. Ethanol analysis in blood samples was based on headspace GC analysis. An alcohol concentration over 0.5‰ determined a positive alcohol record in Studies I to IV and VI.

New LC-MS/MS laboratory methods were developed and validated for measuring concentrations of pregabalin and gabapentin (IV), and naloxone (V).

4 Drug concentration data

The Laboratory of Toxicology provides for all toxicology certificates the whole blood drug concentrations measured, as well as forensic reference concentrations in plasma, on which forensic pathologists base their conclusions as to postmortem whole blood concentrations and these drugs' contribution to death. The forensic plasma reference concentrations (Table 4) are based on published compilations and reports and upon expert opinions on postmortem toxicology.

Table 4. Reference concentrations in plasma available to forensic pathologists, along with laboratory results, for interpretation of postmortem whole blood concentrations.

Drug	Concentration (mg/l) ^a
Buprenorphine	0.5-10
Codeine	0.03-0.1
Fentanyl	1-10
Methadone	0.05-1
Oxycodone	0.01-0.1
Tramadol	ad 0.6
Pregabalin	2.8-8.3
Gabapentin	2-6

^a mg/l otherwise, except µg/l for buprenorphine and fentanyl

To calculate the frequency of different benzodiazepine findings in Studies **I** and **II**, a concentration limit was set to distinguish benzodiazepines from their metabolites. If the concentration of a possible metabolite was less than 10% of the parent-drug concentration, the compound was regarded as a metabolite, and concentrations over 10% implied the parent drug, unless the referral provided more accurate information. This allowed calculation in each case of the number of actual benzodiazepine findings, excluding metabolites.

5 Statistical methods

Drug concentration data were skewed: the concentrations were mainly low, within the therapeutic range, but also some very high concentrations occurred. Due to the skewed data, the medians represented statistics for the concentration data. Difference between groups, such as between abuse and other use, was tested by Kruskal-Wallis and Mann-Whitney tests for independent samples. The statistical analyses tool in Studies **I**, **II**, **V** and **VI** was SPSS 15.0 (SPSS Inc, Chicago, IL, USA), and in Studies **III** and **IV**, IBM SPSS 21.0 (IBM Corp, Armonk, NY, USA).

RESULTS AND DISCUSSION

1 Fatal poisonings

1.1 Opioid poisonings

Since the year 2000, the total number of fatal prescription opioid poisonings in Finland has notably increased (Figure 3). During recent years, opioid poisonings have numbered almost 200 (Figure 3). A case was classified as opioid poisoning if an opioid emerged in laboratory data, and a forensic pathologist had determined the cause of death as poisoning by that opioid. Other opioid-related cases included opioid findings, but the cause of death was other than poisoning. Accidental opioid poisonings usually involve drug abuse, but some poisonings are intentional suicides. The profile of opioid findings has changed during the last decade. Buprenorphine has replaced heroin, and dextropropoxyphene no longer is available in the pharmacies because of its toxicity when combined with alcohol.

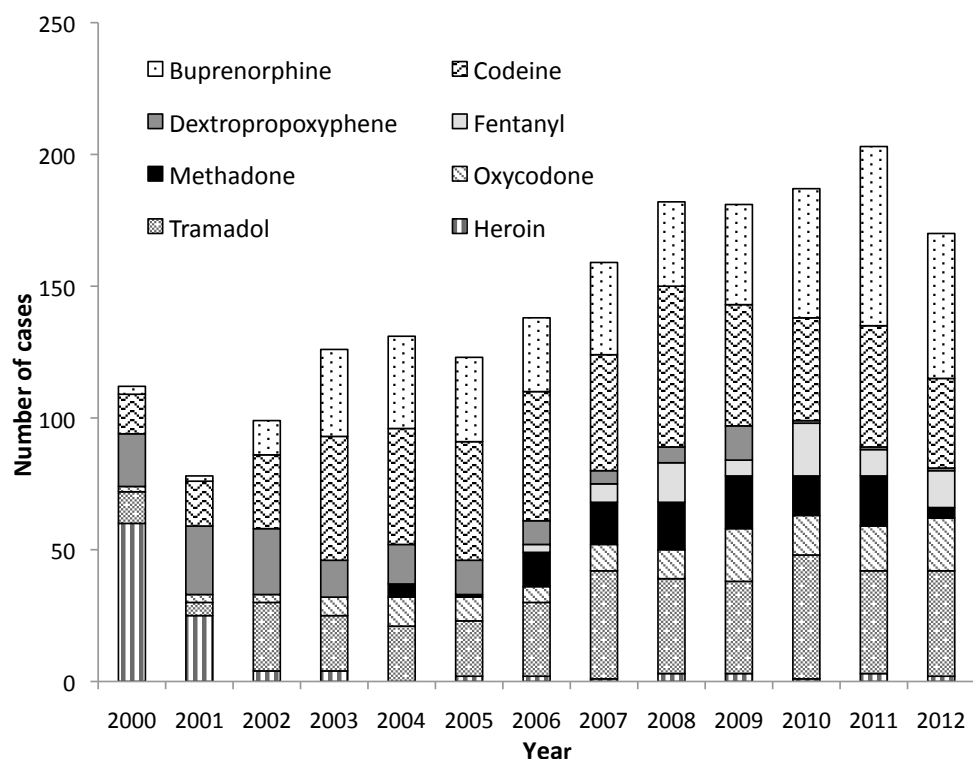


Figure 3. Number of fatal opioid poisonings in Finland 2000-2012, data from the Toxicology Laboratory of the Department of Forensic Medicine, University of Helsinki.

The steep rise in opioid-related deaths among Finns aged 14 to 44 during 2007-2008 seems to have abated during 2010-2011 (Figure 4). Most opioid poisonings proved to be polysubstance poisonings (I, II, Figure 4). During 2000-2008, concomitant opioids were most common in methadone poisonings (27%), followed by tramadol (19%), codeine (15%), and buprenorphine (8%). In codeine and buprenorphine poisonings, concomitant opioids were, however, less frequent than in other codeine and buprenorphine deaths. In 2007-2008, concomitant opioid findings increased markedly (Figure 4).

Findings of benzodiazepines or alcohol >0.5% or of both were connected with 90% or more of the opioid poisonings, and benzodiazepines with 82% (I). Benzodiazepine findings and findings of more than two benzodiazepines were significantly more common in fatal poisonings than in other deaths in codeine, fentanyl, and buprenorphine cases (I), but no statistical difference appeared for methadone (I) nor oxycodone (unpublished data from I). In Sweden during 2005-2010, concomitant benzodiazepines were involved in only 30% of fatal buprenorphine and methadone poisonings [171], markedly less than in this thesis study. Compared to deaths other than poisonings, alcohol findings in tramadol poisonings were less frequent (15%) (I). Alcohol findings were more frequent in buprenorphine (58%) (I) and oxycodone (48%) poisonings than they were in other deaths (unpublished results from I).

In fatal poisonings, median blood concentrations of codeine, tramadol, fentanyl, and oxycodone were over their respective therapeutic upper limits (Tables 4, 5). Buprenorphine and methadone concentrations in fatal poisonings were low, with no clinical difference detectable between poisonings and other cases (I, II, Table 5). Other studies have confirmed these results. In methadone-related deaths in Norway, median methadone concentrations were within therapeutic range, with no significant concentration differences between methadone poisonings and other methadone deaths [91]. A Swedish study confirmed the same findings regarding buprenorphine [178].

To distinguish codeine and tramadol poisonings from deaths other than poisonings, the concentrations of their active metabolites, morphine and *O*-desmethyltramadol, were analyzed. Concentrations of morphine were rather similar both in poisonings and in other cases, but the median codeine/morphine concentration ratio was significantly higher in fatal poisonings (22.5) than in other deaths (5.9) (I). The median concentration of *O*-desmethyltramadol was significantly higher in poisonings (0.8 mg/l) than in other cases (0.2 mg/l), but the concentration ratio tramadol/*O*-desmethyltramadol did not differ significantly between poisonings and other deaths (I).

Accidental overdose was a very typical manner of death in buprenorphine (94%), methadone (94%), and fentanyl (90%) poisonings (I, II, and unpublished data from I). Among oxycodone poisonings, accidental deaths were also common (65%), and in quite a few cases, the manner of death remained unclear (22%) (unpublished results from I). Accidental codeine (43%) and tramadol (55%) poisoning rates were followed by those for suicides (40% of codeine and 31% of tramadol poisonings) (I).

Median age at poisoning was for buprenorphine 27, for oxycodone 28, for tramadol 29, for methadone 30, for fentanyl 31, and for codeine 32, these differences

being statistically nonsignificant (I, in part unpublished). In Sweden in 2005-2010, in contrast, those who died of buprenorphine poisoning were significantly younger (median 28) than were those dying of methadone (35.5) or heroin (34) poisoning [171].

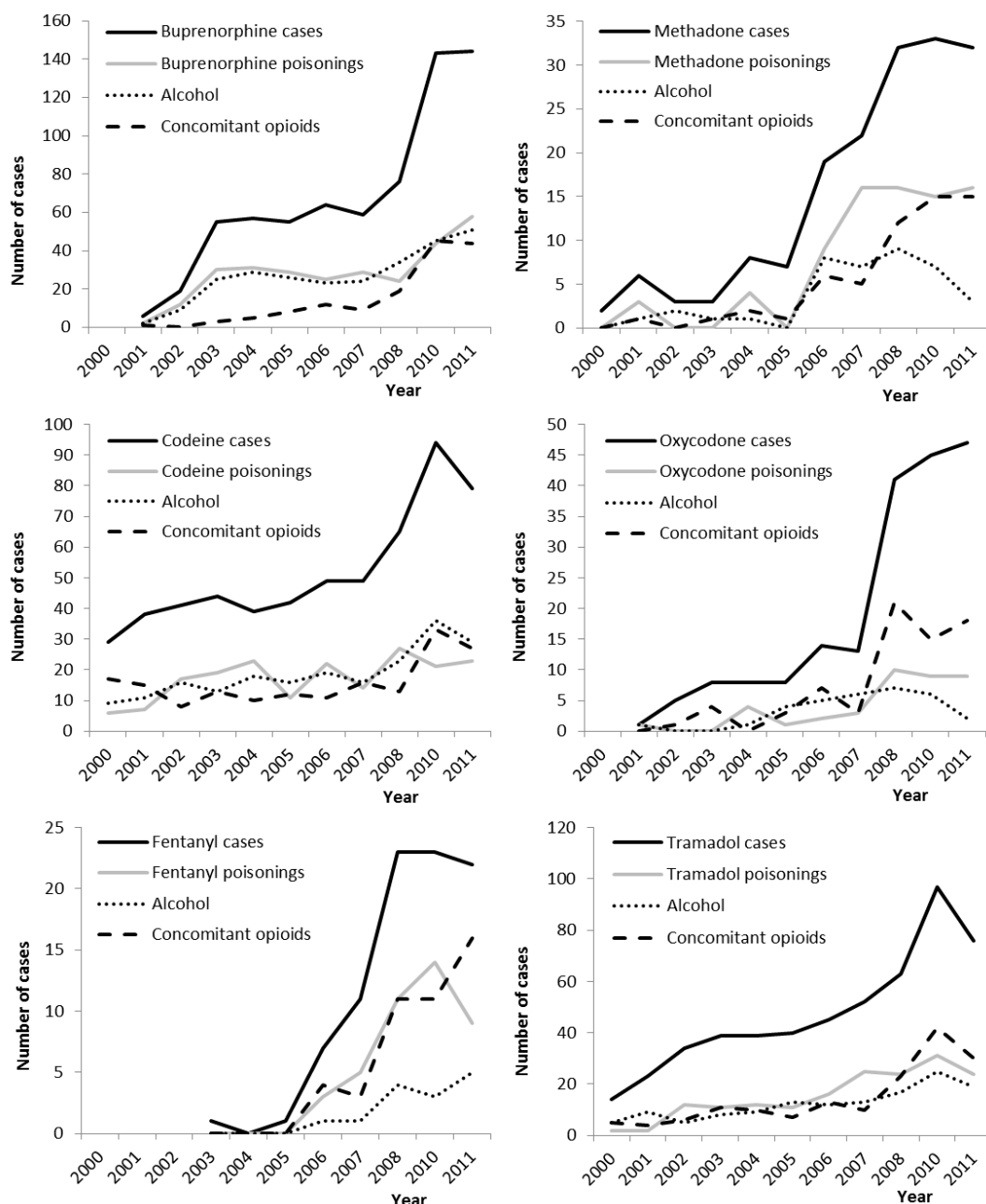


Figure 4. Opioid deaths in age group 14 to 44 during 2000-2011 (data from I, II, III, and unpublished data).

1.2 Buprenorphine poisonings

Of all the 391 buprenorphine cases in 2000-2008, fatal poisonings constituted 47% (II). Buprenorphine deaths were usually delayed and occurred during sleep (II). Death was immediate in 10% of the buprenorphine poisonings, occurring within half an hour of buprenorphine self-administration, whereas death was delayed in 52%, and the course of events remained unknown in 38% (II). Median buprenorphine concentrations in immediate buprenorphine poisonings (3 µg/l) and delayed buprenorphine poisonings (1.2 µg/l) were both situated within the lower half of the therapeutic range, although they differed from each other statistically (II). The blood/plasma ratio for buprenorphine is close to unity [9], implying that buprenorphine plasma and whole blood concentrations are rather similar.

The norbuprenorphine/buprenorphine (NOR/BPN) ratio was lower in the buprenorphine poisonings than other cases, indicating that in such poisonings, death had occurred soon after dosing (II, III). The half-life of NOR is longer than that of BPN (Table 1), which leads to higher NOR concentrations when more time has passed after drug administration. In fatal buprenorphine poisonings, the NOR/BPN ratio was generally <1, and in other causes of death, close to 1 or >1 (II, III). The difference was even more evident when measuring this NOR/BPN ratio in urine (Table 5).

In fatal poisonings, the administration route was mostly parenteral, but in other buprenorphine-related deaths, sublingual. In intravenous buprenorphine administration, no first-pass metabolism occurs, which leads to a lower NOR/BPN ratio than in buccal or sublingual administration.

All but one buprenorphine poisoning included concomitant drugs or alcohol (I, II, III). Buprenorphine poisonings are usually polydrug poisonings. In Sweden, mono-intoxications among the 41 fatal buprenorphine poisonings numbered 4 [178].

Benzodiazepines were involved in 82% of the fatal buprenorphine poisonings (II). One benzodiazepine appeared in 31% of the buprenorphine poisonings, two in 36%, and three or four in 15%. The most frequent benzodiazepines were alprazolam, diazepam, temazepam, and oxazepam (II). In Sweden, 75% of buprenorphine poisonings included hypnotics or sedatives, most frequently alprazolam (in 41% of the buprenorphine poisonings) [178]. The median concentration of alprazolam in Study II (0.06 mg/l) was slightly higher than its upper therapeutic limit of 0.05 mg/l [179], but the other median benzodiazepine concentrations remained within their therapeutic ranges (II). These results are in concordance with the Swedish study reporting that alprazolam concentrations were in the upper half or above the therapeutic range, whereas diazepam and other benzodiazepine concentrations were lower [178].

Although benzodiazepines and alcohol in buprenorphine poisoning, compared to their occurrence in other deaths, were more common, concomitant opioids were rather rare: during 2000-2008, 92% of the buprenorphine poisonings included no concomitant opioids, and only one additional opioid was present in the remaining 8% (II). This was significantly lower than the figure of 21% of concomitant opioids in other buprenorphine deaths (II). When other opioids were present, their concentrations were lower in buprenorphine poisonings than in other cases (II). During 2010-2011, concomitant opioids in buprenorphine poisonings of those deceased aged 14 to 44 (23%) were less common than in other buprenorphine-

related deaths (36%) (unpublished results from **III**), although the percentage of concomitant opioids had almost tripled since 2000-2008.

1.3 Benzodiazepine poisonings

In Studies **I** and **II**, of the 1,363 opioid-positive cases, 1,022 included benzodiazepines, and only 34 cases were classified as benzodiazepine poisonings, leading to a benzodiazepine poisoning proportion of 3.3%. Alprazolam poisonings were mostly accidents (14/20), and zopiclone and zolpidem poisonings, suicides (8/14). Alprazolam poisonings were connected with buprenorphine, amphetamine, and cannabis use, whereas zopiclone and zolpidem poisonings mainly included the weak prescription opioids codeine, tramadol, and dextropropoxyphene, as well as other prescription psycholeptics. (Unpublished results from **I**, **II**)

Table 5. Comparison of findings and opioid concentrations (C) in fatal poisonings among those deceased aged from 14 to 44 years among Studies **I**, **II**, **III**, and **VI**.

		Abuse cases	Poisonings (%)	C (mg/l) ^a , poisoning	C (mg/l) ^a , other
2000-2008 (I , II)	Buprenorphine	391	182 (46.5)	1.4*	1.2*
	NOR/BPN ratio	291	182 (-)	0.56*	1.16*
	Methadone	102	48 (47.1)	0.35	0.30
	Codeine	360	146 (40.6)	1.4*	0.09*
	Tramadol	348	117 (33.6)	5.3*	0.6*
	Fentanyl ^b	43	20 (46.5)	15*	4.6*
	Oxycodone ^b	98	21 (21.4)	0.28*	0.08*
	Benzodiazepines ^b	1,022	34 (3.3)	-	-
2010-2011 (III)	Buprenorphine, blood ^b	251	107 (42.6)	1.3	0.97
	Buprenorphine, urine ^b	245	81 (33.1)	51*	21*
	Methadone ^b	54	29 (53.7)	0.50	0.40
	Codeine ^b	92	33 (35.9)	1.4*	0.14*
	Tramadol ^b	108	55 (50.9)	5.6*	0.8*
	Fentanyl ^b	28	24 (85.7)	8.1*	3.4*
	Oxycodone ^b	29	14 (48.3)	0.38*	0.12*
1/1/2010- 30/6/2011 (VI)	Buprenorphine, blood ^b	213	66 (31.0)	1.2*	0.66*
	Buprenorphine, urine ^b	211	67 (31.8)	83*	25*
	NOR/BPN, blood ^b	193	60 (31.1)	0.65	0.85
	NOR/BPN, urine ^b	214	65 (30.4)	0.20*	1.23*

^a postmortem blood concentrations unless stated otherwise; in mg/l, except in µg/l for buprenorphine and fentanyl

^b unpublished concentration data

* denotes a statistically significant difference in concentration medians between poisonings and other cases, p<0.05.

1.4 Gabapentinoid poisonings

During 2010-2011, pregabalin findings numbered 316 and gabapentin 43 (IV). Fatal poisonings were somewhat rare: poisonings comprised 10% of all the pregabalin- and 5% of the gabapentin-related deaths (IV). Of the drug-abuser cases, pregabalin poisonings involved 19% and gabapentin poisonings 13% (IV). Concentrations in gabapentinoid poisonings were high. Forensic pathologists may have considered pregabalin and gabapentin safe substances somewhat similar to benzodiazepines, possibly partly because individuals have survived very high gabapentinoid concentrations. If an opioid was found, which was the case in about 90% of the gabapentinoid poisonings (IV), the opioid had usually been considered the main cause of death and gabapentinoid a contributory factor, unless its concentration was very high. This is in concordance with another postmortem study of pregabalin cases in which, of 15 pregabalin-related deaths with reported peripheral blood concentrations, 2 were polydrug poisonings with pregabalin as the main toxin [180]. In these pregabalin poisonings, its concentrations in peripheral blood were high: 206.7 and 45.3 mg/l, whereas the median pregabalin concentration in all cases was 6.4 mg/l [180].

Pregabalin was present in a quarter of fatal opioid poisonings (Table 6). It was a common finding in codeine- and tramadol-abuser cases, which may be connected to the fact that all the three of these are easily prescribed with normal prescription practices.

In the abuser cases in fatal pregabalin poisonings, pregabalin median concentration, 29.5 mg/l, was higher than the median 15 mg/l for abuser cases overall, and, compared to its therapeutic range, clearly above it (Table 4). Only one case of gabapentin poisoning was attributed to drug abuse, and the gabapentin concentration in that case, 45 mg/l, was markedly higher than the median concentration of 12 mg/l in all gabapentin abuse cases (unpublished result from IV).

Table 6. Pregabalin (PRG) findings in fatal opioid poisonings (unpublished data from III, IV).

	All fatal opioid poisonings		Drug-abuser cases	
	Fatal poisonings	PRG findings (%)	Fatal poisonings	PRG findings (%)
Buprenorphine	117	29 (24.8)	114	27 (23.7)
Codeine	87	16 (18.4)	33	11 (33.3)
Fentanyl	28	3 (10.7)	25	3 (12.0)
Methadone	34	11 (32.4)	34	11 (32.4)
Oxycodone	33	6 (18.2)	16	2 (12.5)
Tramadol	86	30 (34.9)	56	25 (44.6)
Total	387	95 (24.5)	278	79 (28.4)

2 Prescription opioid and gabapentinoid abuse

2.1 Abuser profiles

The proportions of drug-abuser cases among all cases related to each drug were for buprenorphine 86%, for methadone 82%, for tramadol 29%, for codeine 16%, for fentanyl 15%, for oxycodone 7%, for pregabalin 48%, and for gabapentin 19% (Figure 5).

Abusers were aged 18 to 74 years. The median age in the abuser group ranged from 30 to 35, and among users who were not abusers, from 47 to 75 (III, IV). Buprenorphine-, fentanyl-, pregabalin- and gabapentin abusers were the youngest, median age 30, whereas the median age of tramadol abusers was 32, and codeine-, methadone-, and oxycodone users were the oldest, median 35. Men dominated both the abuser- and other-user statistics (76% of codeine and 75% of gabapentin abusers, and of other abusers of opioids and pregabalin, 84-87%). Drug abusers were, then, mainly young men. (III, IV)

Fatal poisonings were more common in opioid-abuser deaths than in other deaths, the proportions of fatal poisonings ranging from codeine-abusers' 27% to the fentanyl-abusers' 78%. Poisonings caused by abuse of pregabalin (19%) or gabapentin (13%) were less frequent. The proportion of accidental deaths of abusers ranged from 65% in codeine deaths to 84% for fentanyl. (III, IV)

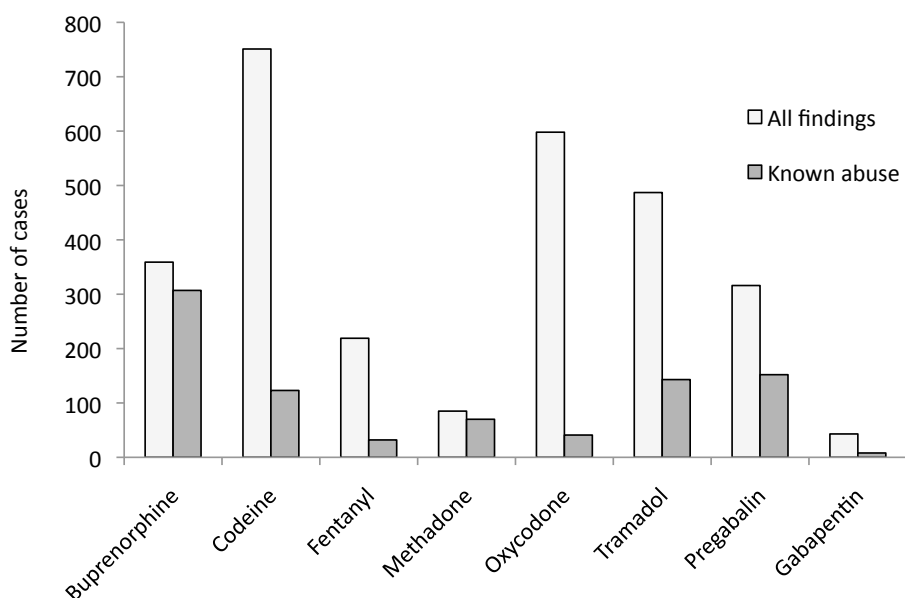


Figure 5. Proportion of abuse findings among all findings for opioids and gabapentinoids in medico-legal cause-of-death investigations in Finland during 2010-2011 (III, IV). Drug abuse refers to cases which involved drug abuse as narcotics.

Buprenorphine and methadone concentrations in abuser deaths were low, only 1.2 µg/l for buprenorphine and 0.40 mg/l for methadone (III). Buprenorphine and methadone findings concentrated in younger age groups, and these two drugs were mostly abused (Figure 6). Fentanyl abuser deaths proved to be mainly related to accidental poisonings, and the median abuse concentration, 8.2 µg/l, fell within the reference plasma concentration range, although near the upper limit (Table 4). Unlike other strong opioids, the median concentration of oxycodone in abuser cases, 0.24 mg/l, was 2.4 times as high as its therapeutic limit (III). Oxycodone abuse was rare, but when abused, it was attributed to polyopioid abuse, including concomitant opioids in 56% of the abuse cases (III). Consistent with these findings, oxycodone abuse has been suspected to involve rather disadvantaged polydrug abusers using whatever drugs they could get their hands on [181]. Pregabalin and tramadol showed considerable abuse among the youngest age groups (Figure 6).

Approximately 90% of the pregabalin- and gabapentin-abuser cases included opioids (IV), and among opioid-related deaths, 26% of the opioid-abuser cases involved gabapentinoids (unpublished data from III, IV). This proportion is of the same magnitude as in a recent report on methadone maintenance treatment showing gabapentinoid abuse to be present among 22% of the patients [57]. Cases of driving under the influence of drugs in Finland have also revealed recreational pregabalin use concomitantly with that of other psychoactive drugs [125].

The median abuse concentrations for weaker drugs were higher, above their therapeutic ranges (Table 4): for tramadol 3.1 mg/l, for pregabalin 15 mg/l, for codeine 0.27 mg/l, and for gabapentin 8.3 mg/l (III, IV). Consistently, gabapentinoid abusers have been shown to take these drugs at doses clearly exceeding clinical recommendations [182].

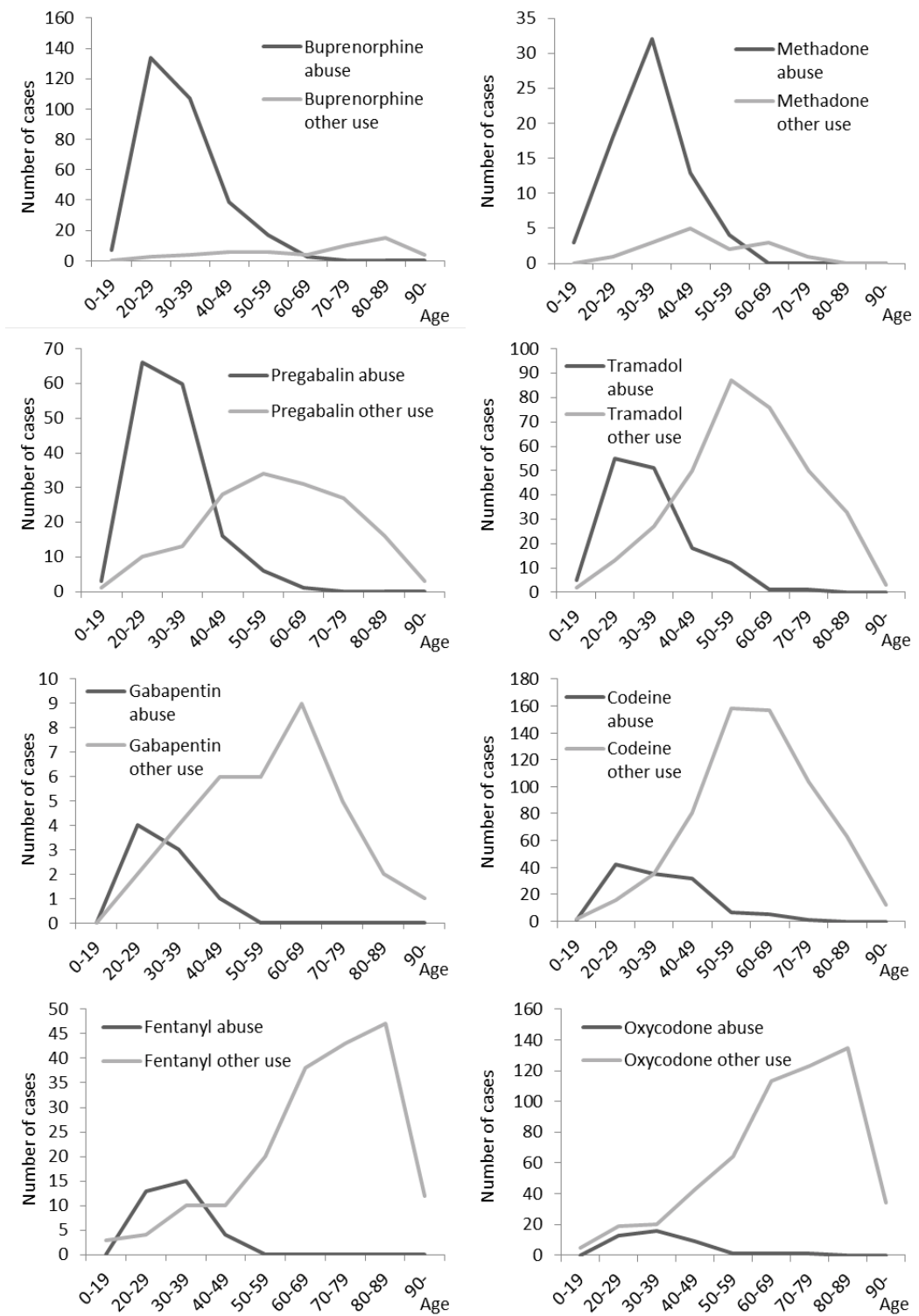


Figure 6. Comparison between abuse versus other use of opioids and gabapentinoids (III, IV).

2.2 Concomitant alcohol and opioid findings

All abuser cases included drugs acting on the CNS other than opioids or gabapentinoids. Among the abuser cases, proportions of concomitant opioid findings were for buprenorphine 32%, for methadone 49%, for tramadol 50%, for codeine 53%, for fentanyl 56%, for oxycodone 56%, for pregabalin 91%, and for gabapentin 88% (III, IV). Codeine-, oxycodone-, and tramadol-abuser cases involved concomitant opioids significantly more often than did other than abuser cases.

Alcohol abuse is in Finland more common than in many other countries [27], a fact paralleled by Finland's opioid-abuser deaths. Among opioid abusers, alcohol was involved in 31% of the deaths, whereas in the United States in 2010, alcohol was involved in 22% of deaths related to opioid pain-reliever abuse [183]. Among the abuse cases in this thesis study, proportions of positive alcohol findings were for buprenorphine 35%, for codeine 33%, for fentanyl 28%, for tramadol 25%, for methadone 17%, for oxycodone 12%, for pregabalin 16%, and for gabapentin 22% (III, IV). Alcohol findings among abusers compared to other users were more frequent among buprenorphine, codeine, and fentanyl cases. Abuser profiles between Finland and the United States differed also here: among the opioids studied in this thesis, in the United States oxycodone involved alcohol the most (23%) [183], but in the Finnish data, oxycodone deaths included the fewest concomitant alcohol findings (III).

3 Buprenorphine-naloxone abuse

3.1 Naloxone concentrations in OMT patients

Before their entering OMT, all the patients' urine samples tested positive for buprenorphine at a median of 90 µg/l. The urine naloxone concentration ranged from 0 to 300 µg/l, six of them being 0 µg/l. During OMT with BNX, all samples of the 32 OMT patients were positive for naloxone. In the stable phase of OMT, the naloxone median was 60 µg/l and its range, 5 to 200 µg/l. In the unstable phase, the naloxone median was 70 µg/l and range 10 to 1700 µg/l. Median urine naloxone concentrations differed statistically significantly between patients before and during OMT, but not between the stable and unstable phase in the treatment. (V)

In the "high naloxone group", where naloxone (NX) was above 200 µg/l, the median NX/BPN ratio was 0.9 and NOR/BPN ratio 1.8, and in the "low naloxone" group, with $NX \leq 200$ µg/l, the median NX/BPN ratio was 0.3 and NOR/BPN 4.5 (V). NX has considerable first-pass metabolism and very low oral and sublingual bioavailability, which leads to low NX concentrations in sublingual administration. Moreover, timing of the urine sample collection influences these ratios and their interpretation. A high NX/BPN ratio may imply recent BNX intake because the half-life of NX is shorter than that of BPN. Concentrations of NX and BPN become lower when time has passed after drug administration, with NOR concentration remaining high longer. In Study V, no information was available as to drug-administration time compared to sampling time. Patients in the stable phase of OMT should have taken their medications once a day, but the suspected BNX abusers may also have taken extra doses.

In the stable phase, 85% of the urine naloxone concentrations were below 100 µg/l (5 to 90 µg/l), whereas in the unstable phase, 33% contained naloxone over 100

µg/l (V). Hull et al. studied 216 urine samples from 70 patients receiving 8 to 24 mg BNx a day and found that in unadulterated samples, urine naloxone concentration was undetectable, with the cut-off 100 µg/l [184]. Based on this and the findings in Study V, a threshold of urine naloxone higher than 100 µg/l is suggested to indicate parenteral BNx use (VI). An NX/BPN concentration ratio close to or >1, and NX concentration above 100 to 200 µg/l, may differentiate parenteral BNx use from sublingual use, in which NX/BPN ratio and NX concentration are low.

3.2 Buprenorphine-naloxone poisonings

Based on laboratory findings from OMT patients, the 225 buprenorphine-related deaths were classified into three groups: parenteral BNx (urine NX>100 µg/l), parenteral buprenorphine (BPN>50 µg/l and NX 0 µg/l), and other BNx or BPN (NX≤100 µg/l, or BPN≤50 µg/l and NX 0). The contribution by parenteral BNx abuse was 12% of all the buprenorphine-related deaths (VI). Intravenous BNx has been successful in reversing acute opioid overdose [185], but Study VI showed that intravenous abuse of BNx may be fatal. Buprenorphine poisonings were proportionally even more common in the parenteral BNx group (68% of parenteral BNx cases) than in the parenteral BPN group (31%) (VI). In fatal buprenorphine poisonings, the proportion of parenteral BNx abuse was 28% (VI). The median NOR/BPN ratio was significantly higher among “Other BNx or BPN” (1.26) than in “Parenteral BNx” (0.22) or “Parenteral BPN” (0.26), suggesting that the death had occurred more rapidly after drug administration in the parenteral groups, and in the other-use group, death was delayed (VI).

French researchers have concluded that in rats, intravenous BNx use may improve buprenorphine safety because naloxone prevents the dose-dependent respiratory depression toxicity of norbuprenorphine [114]. The differences in respiratory effects between BNx and BPN were, however, significant only in combination with diazepam; in that case, respiratory depression rose in opioid-naïve rats, but fell in buprenorphine-tolerant rats [115]. This means that BNx may contribute less to respiratory depression in a tolerant BNx user who also takes benzodiazepines, which, according to Study II, is a highly common practice. The impact of naloxone in reducing respiratory depression may, however, not be clinically high enough, since fatal buprenorphine poisonings were proportionally more common among BNx abusers than among BPN abusers (VI).

GENERAL DISCUSSION

Traditionally, opioid poisonings are seen as overdose deaths resulting from a too-large dose of the drug. Because prescription opioids are manufactured by pharmaceutical companies with the drug content printed on the package, they are in this sense better defined than, for example, illicit heroin. Prescription opioids are, however, never a safe alternative in drug abuse. Their abuse may be fatal, even at concentrations within their therapeutic ranges. Factors related to opioid deaths include polydrug use involving other CNS-depressant drugs or alcohol (**I**, **II**), and low physical activity: opioid poisonings often are delayed, occurring during sleep (**II**). In unintentional fatal drug poisonings, prescription opioids are the most important group of medicines found, often involving drug abuse. Knowing the characteristics of drug abuse is vital in preventing its undesirable consequences.

Unlike with many other drugs, the correlation between opioid blood concentration and fatal outcome is low. Opioid concentrations themselves are, therefore, insufficient in determining opioid poisonings. Concentrations in both buprenorphine poisonings and other abuser cases were low and did not differ much between poisonings and other opioid-related deaths (**II**). Swedish researchers also showed that no lethal buprenorphine blood concentration can be defined [178]. Buprenorphine poisonings undoubtedly occur, although no rigid fatal-concentration limits exist. In distinguishing poisonings from other deaths, tools worth consideration include metabolite concentrations and parent/metabolite concentration ratios (**I**). Urine NOR/BPN concentration ratios provided the most evident difference between poisonings and other buprenorphine deaths (**I**, **VI**). The main factors influencing such concentration ratios are administration route, genetic polymorphisms, and time of death and of sampling. In oral administration, first-pass metabolism may produce more metabolic products than in parenteral administration. Information on CYP2D6 genotype would improve interpretation of the parent/metabolite ratios of codeine and tramadol, because slow CYP2D6-metabolizers produce fewer metabolic products of codeine and tramadol. In some drug intoxications, in addition, high drug doses may produce autoinhibition, leading to a lower ratio of metabolic products, although this has not been detectable among opioids.

Because urine samples undergo routine toxicological screening and quantification of drugs of abuse, knowing the urine NOR/BPN concentration could help forensic pathologists to determine whether a death was poisoning, despite the low buprenorphine concentration. Low postmortem buprenorphine and methadone concentrations characterized both abuse cases and other cases (**I**, **II**, **III**). Forensic pathologists determine the cause of death not only according to drug concentrations, but according to all available documents and autopsy data, including background information. In contrast to stronger opioids, concentrations of codeine and tramadol among both abusers and other users were above their therapeutic ranges (**I**, **III**). High drug concentrations may suggest an oral administration route, and low concentrations may suggest intravenous administration, because the rapid increase in systemic concentrations of opioids with intravenous dosing can be more toxic than

their more gradual increase after oral dosing. Iwersen-Bergmann et al. showed that among methadone-related deaths, mean methadone concentrations were one-third lower in the injecting group [186]. In another study, plasma concentrations of tramadol after intravenous administration were higher than after oral administration, but after intravenous administration, substantially less increase occurred in the concentrations of tramadol's active metabolite *O*-desmethyltramadol; the reason is that after intravenous administration, no first-pass metabolism occurs [187]. This suggests that after intravenous intake, the tramadol/*O*-desmethyltramadol ratio would be high. In rats, blood tramadol/*O*-desmethyltramadol ratios in an oral administration group and in an intravenous group were, respectively, 2 and 20 [188]. In Study I, median tramadol/*O*-desmethyltramadol ratios in fatal poisonings and other-than-fatal poisonings were 7.7 and 6.4, suggesting that tramadol administration was mostly oral.

Postmortem fentanyl concentrations seem somewhat lower after intravenous than after transdermal or transmucosal administration. Postmortem fentanyl concentration has been lower when it was administered intravenously (mean 8 µg/l, range 5-10 µg/l, n=3) than transdermally (mean 21 µg/l, range 10-38, n=6) [83]. Postmortem femoral blood concentrations after intravenous administration have been in other studies 2.7 µg/l and 13.8 µg/l [189], and 13 µg/l [190]. In transdermal administration, case reports have revealed a postmortem femoral blood concentration of 17.2 µg/l [191], and in transmucosal cases, of 13, 19, 28, and 97 µg/l [192]. Martin et al. found, in contrast, that postmortem fentanyl concentrations were higher following intravenous (mean 53 µg/l, range 3-383 µg/l, n=12) than transdermal (mean 15 µg/l, range 3-71 µg/l, n=62) administration [193]. In their material, however, of 12 intravenous administration cases, 10 were fentanyl poisonings, compared to only 27 of the 64 transdermal cases [193], and in fatal poisonings, drug concentrations usually are higher than in other drug-related deaths. In addition, the concentration range in intravenous cases was wide, causing a bias in the mean; the median in the intravenous cases was 20 µg/l and in the transdermal cases 12 µg/l [193]. Clinical concentrations following intravenous fentanyl administration are high, but they decline within 1 or 2 hours, whereas transmucosally or transdermally administered fentanyl reaches its peak concentration more slowly and steadily [96]. Opioid poisonings are usually delayed, so intravenously administered opioid concentrations are not peak concentrations but may have decreased substantially, even in fatal opioid poisonings. Postmortem concentrations may help in differentiating routes of administration, although concentration data are insufficient without more background information, because low concentrations may also result from inadequate or no tolerance, or from delayed death.

This study revealed that at least 0.5% of all the deceased in Finland during 2010-2011 had abused opioids as narcotics (III). The figure is close to the estimate of 0.38 to 0.45% from 2012 based on data collected from various health care registers [135]. These rather similar results suggest that comprehensive postmortem database studies can also serve in the process of estimating abuse among the living. Surveys based on questionnaires provide information on the prevalence of drug abuse, but they suffer from low reliability of answers and poor response rates. Ethnographic studies provide information on characteristics of drug abuse, but they are time-consuming and lack prevalence information. Studies from adverse databases suffer from

underreporting. Prescription database studies exclude over-the-counter products, illegal drugs, and medications purchased from treatment units as is most buprenorphine and methadone consumed in OMT. Various registers from health care in Finland are available, but collecting and unifying data from these registers is highly time-consuming, difficult, and requires several ethics-committee approvals. By contrast, postmortem toxicology information in Finland comes from one comprehensive database. With properly designed study protocols, postmortem database studies could be produced even annually with considerably less work than needed for register studies or surveys.

Regularly published lists of postmortem drug findings provide information on fatal drug poisonings and drug findings in general. These data reveal trends in drug use both in fatal poisonings and in drug occurrence. An increase in fatal drug poisonings and drug findings does not necessarily implicate rising drug abuse, because many of the illegally used drugs are also widely used as legal, prescribed medications. Studies **III** and **IV** combine toxicology laboratory results and individually collected information from each death certificate to estimate the proportion of drug abuse. In Finland, where about 13% of all deaths undergo toxicological analysis annually, postmortem data can provide estimates of problem drug use among the entire population. Postmortem toxicology among the young deceased is common in Finland and involves 60 to 70% of them [92]. Studies **III** and **IV** revealed the minimum number of opioid- and gabapentinoid-abuser cases. The proportion of opioid use other than abuse was, however, impossible to estimate, because the elderly, more often on prescribed and properly used medication, undergo toxicological cause-of-death investigation less often than do young abusers.

Buprenorphine-naloxone, in addition to buprenorphine, involves wide abuse. This thesis study reveals that BNX may, in accidental poisonings, be fatal even more often than buprenorphine (**VI**). Other key findings were the high abuse proportion of pregabalin and tramadol, and the high prevalence of opioids in pregabalin deaths (**IV**). The abuse potential of pregabalin and tramadol has been noticed in another Finnish study, as well [194]. In Study **III**, tramadol differed somewhat from other medicinal opioids. Its abuse percentage was only 29%, compared to abuse proportions for buprenorphine and methadone of over 80% (**III**). Tramadol use in Finland is, however, quite common, and of all the abuse cases, tramadol accounted for 20%, being in number of cases the second most abused opioid (**III**). Tramadol seizures by Finnish Customs have increased markedly [124], which would likely indicate increasing tramadol abuse. Deaths involving tramadol abuse usually involve polydrug use [195], consistent with the findings in this thesis. Tramadol poisonings included more benzodiazepines than did other tramadol-related deaths (**I**), and tramadol abuse included more concomitant opioids than did other tramadol deaths (**III**). Potential pharmacokinetic and pharmacodynamic interactions between tramadol and other drugs may enhance these drugs' toxicity and lead to a fatal outcome.

Findings concerning the abuse liability of tramadol are somewhat contradictory. When tramadol came onto the market, it was suggested to have little abuse potential [196-200], but other studies call it considerable [195,201,202]. Because of tramadol's atypical character as an opioid and its effects on serotonin and noradrenalin reuptake besides its opioid activity, its abuse potential, dependency, and complications via opioid-receptor effects have been considered low, making it

recommendable as a safe drug compared to other opioids [196]. In animals, tramadol produces drug-seeking behavior [116], but the abuse potential of tramadol in animals has been less than that of typical opioids. In humans, its oral, but not parenteral, administration has produced opiate-like effects [199]. Because tramadol elicits only modestly positive subjective effects, it has been judged as only rarely useful as a highly desirable euphoriant [199]. One German expert committee has recently found a low potential for its misuse, abuse, or dependency [200]. Tramadol may well act as a less preferably abused drug compared to other opioids. Oral tramadol has, however, a reinforcing efficacy in prescription opioid abusers, leading to risk for abuse [202]. Among recreational-drug users, oral tramadol has abuse-liability effects [201].

Reasons for drug abuse include not only a search for euphoria. For most drug abusers, getting high is the primary initial motive, but as drug abuse continues, the motive evolves into avoidance of withdrawal symptoms [203]. Besides getting high, motivations for non-medical prescription-drug abuse also include coping with stress, moderating other drugs' effects, experimentation, and pain relief [203,204]. In this context, it seems obvious that tramadol also has marked abuse potential, although its effects were weaker than those of stronger opioids. Tramadol abuse is a health problem that needs more preventive action in Finland, as well.

Weak opioids and gabapentinoids may not be the first-line drugs of abuse, but they are abused, for example, in boosting opioid effects. Opioids or gabapentinoids are not the drugs of choice for patients with drug addiction or a drug-abuse history. Gabapentinoids should be excluded from use for drug addicts and abusers with, for example, neuropathic pain resulting from limb amputations; other, less-addictive medications are available. Doctors should pay special attention to opioid and gabapentinoid prescriptions. One should carefully inspect for signs of injecting and signs of drug abuse. Doctors should receive training in avoiding those medicinal products that abusers prefer, and in minimizing the ever-present abuse risk when prescribing opioids. This training could include a choice between short- and long-acting products, and the types of packages and products abusers especially prefer. For example, tramadol is available in short-acting capsules which are quite easy to open and dilute in water, when compared to slow-release hard tablets. Opioids and gabapentinoids should be prescribed in primary health care only for valid indications and short periods. For drug addicts, treatment against pain other than medications may be preferable [205].

The cooperation of health care and forensic professionals is vital in identifying and implementing preventive strategies against drug abuse [206]. Medical practitioners should be cautious with drug prescriptions, and forensic pathologists should provide more consistent and detailed information on prescription drug use [206]. Investigation of deaths of suspected drug abusers and deaths suspected to relate to poisonings or to traumatic accidents should always include postmortem toxicology, which will ensure rather reliable estimates of drug-abuser deaths.

Conclusions based on postmortem laboratory data are, however, far from complete, even were the rate of postmortem toxicology high. Determining whether a case involved drug abuse was based on referrals and death certificates issued by forensic pathologists, and then the relevant information may have been in some cases very scarce. Improvements for research purposes would include a more accurate patient history from forensic pathologists to be shown in referrals and death

certificates. In Study V, combining laboratory data on postmortem samples with samples from known drug users, along with proper background information, assisted in interpretation of laboratory analysis results; this helped to distinguish drug abuse from other use. New laboratory analytics also require attention: German researchers have created laboratory methods measuring disaccharides in urine samples to determine intravenous methadone or buprenorphine abuse [186,207]. Combining such laboratory analyses with regular drug toxicology data would surely improve postmortem abuse studies and more easily provide information on drug abuse than do studies based on combined register data.

According to the Decree of the Ministry of Social Affairs and Health on Prescription of Medicines (1088/2010), special attention should be directed at prescription of medications with addiction potential [208]. Policy-makers should, however, notice that directions for safe prescriptions are insufficient to prevent drug abuse. Although directions for benzodiazepine prescribing already exist, prescription benzodiazepines are still widely abused. To prevent drug dependence, a doctor should monitor each patients' drug use [208]. This monitoring could include questionnaires regarding medication benefit and harm, patient data from earlier treatment periods and from other treatment units, and urine drug screening [209]. Such screening should be more easily available and performed, even before suspicion of drug abuse arises. Gudin et al. suggest routine urine toxicology testing, including opioids, benzodiazepines and ethanol biomarkers, for all patients receiving opioid medication in pain management [210]. New, cost-efficient urine drug screening methods are already available, methods that allow simultaneous screening and confirmation both of conventional drugs of abuse and of new psychoactive substances. They show performance far beyond that of a conventional immunoassay [211]. Resources in primary health care must be sufficient for doctors to be able to properly follow all suggestions for safer prescribing.

CONCLUSIONS

The typical death of a Finnish opioid abuser is an accidental, delayed polydrug poisoning involving opioids, gabapentinoids, benzodiazepines, alcohol, or other psycholeptics. The victim is typically a male in his thirties. Compared to the period 2000-2008, in 2010-2011, the frequency of concomitant alcohol and opioid findings for fatal opioid poisonings increased. During 2010-2011, concomitant opioids were associated with half the abuser cases involving opioids other than buprenorphine, and almost a quarter of the buprenorphine cases. Codeine and tramadol, in particular, were involved in polydrug use, with more additional benzodiazepines in poisonings than in other deaths, and in abuser cases, more concomitant opioids. Opioids played a significant role in pregabalin- and gabapentin-abuser deaths: almost all of these included opioids.

In opioid poisonings, postmortem blood drug concentrations may be low, and they may alone be insufficient for determining cause of death; proper background information in addition to concentration data is necessary. Codeine, tramadol, pregabalin, and gabapentin concentrations among drug abusers in fatal poisonings were generally higher than their therapeutic upper limits. Median buprenorphine and methadone concentrations fell within their therapeutic ranges, rather similar between poisonings and other deaths, as well as between abusers and other users. For some opioids, concentrations of their metabolites or concentration ratios of the parent and metabolite may prove more useful than mere parent concentrations, although concentration ratios also overlap between poisonings and therapeutic cases. In buprenorphine poisonings, the norbuprenorphine/buprenorphine ratio was low. In codeine poisonings, the concentration ratio of codeine/morphine was high. Tramadol poisonings were associated with high concentrations of tramadol's active metabolite *O*-desmethyltramadol.

Abuser cases among all deceased opioid and gabapentinoid users, as well as fatal opioid poisonings, were concentrated in young to middle-aged men. Buprenorphine and methadone findings were most often associated with abuse. Pregabalin and tramadol, as well, appeared in a considerable proportion of abuse cases. The proportion of tramadol poisonings among all tramadol-related deaths in abuser cases from 2000-2008 increased during 2010-2011 by a third, and the proportions of fentanyl and oxycodone poisonings doubled. Fentanyl abuse was rather rare but seemed especially dangerous, because a great majority of the fentanyl-abuser deaths were accidental overdoses.

Despite the opioid antagonist naloxone, parenteral BNX abuse was commonly related to fatal buprenorphine poisonings, proportionally even more than was the case with the abuse of buprenorphine. Buprenorphine and naloxone concentrations measured in urine can diagnose parenteral BNX abuse. Although naloxone was measurable also in sublingual BNX use, its concentration remained low. The urine naloxone/buprenorphine concentration ratio provided an abuse indicator for BNX, a high ratio suggesting parenteral BNX abuse.

Finland's comprehensive, constantly enlarging postmortem toxicology database provides information for forensic medicine, public health, and clinical medicine. Finland's high postmortem toxicology rate allows detection of drug poisonings and more accurate cause-of-death investigation. These data produce, moreover, prevalence data through drug findings and reveal emerging trends in both prescription-drug and illegal-drug use settings. Recognizing drug-abuse trends can enable appropriate drug regulation and enforcement that should have a positive impact on morbidity and mortality. Analytical laboratory methods for measuring drug concentrations as well as conclusions based on concentration data are applicable also for monitoring medication compliance among living patients.

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REFERENCES

- [1] E. Vuori, I. Ojanperä, T. Launiainen, J. Nokua, R. Ojansivu, Myrkytyskuolemien määrä on kääntynyt laskuun [Fatal poisonings in Finland during 2008-2010 (in Finnish, English summary)], *Finnish Med J.* 67 (2012) 1735-1741.
- [2] International cooperation against the world drug problem: Resolution adopted by the General Assembly on 18 December 2013, A/RES/68/197, UN General Assembly, https://www.unodc.org/documents/commissions/CND/Drug_Resolutions/2010-2019/2013/A_RES_68_197.pdf, accessed on May 15, 2014.
- [3] Perspectives on drugs - The EU drugs strategy (2013–20), European Monitoring Centre for Drugs and Drug Addiction, <http://www.emcdda.europa.eu/topics/pods/eu-drugs-strategy-2013-20>, accessed on May 15, 2014.
- [4] G.G. Davis, National Association of Medical Examiners and American College of Medical Toxicology Expert Panel on Evaluating and Reporting Opioid Deaths, Complete republication: national association of medical examiners position paper: recommendations for the investigation, diagnosis, and certification of deaths related to opioid drugs, *J Med Toxicol.* 10 (2014) 100-106.
- [5] R.B. Raffa, Basic pharmacology relevant to drug abuse assessment: tramadol as example, *J Clin Pharm Ther.* 33 (2008) 101-108.
- [6] K.T. Olkkola, V.K. Kontinen, T.I. Saari, E.A. Kalso, Does the pharmacology of oxycodone justify its increasing use as an analgesic? *Trends Pharmacol Sci.* 34 (2013) 206-214.
- [7] A. Ferrari, C.P. Coccia, A. Bertolini, E. Sternieri, Methadone – metabolism, pharmacokinetics and interactions, *Pharmacol Res.* 50 (2004) 551-559.
- [8] F. Paille, H. Martini, Nalmefene: a new approach to the treatment of alcohol dependence, *Subst Abuse Rehabil.* 5 (2014) 87-94.
- [9] R.C. Baselt, Disposition of toxic drugs and chemicals in man, Tenth edition, Biomedical Publications, Seal Beach, California, 2014.
- [10] J.J. Kuhlman Jr, S. Lalani, J. Magluilo Jr, B. Levine, W.D. Darwin, Human pharmacokinetics of intravenous, sublingual, and buccal buprenorphine. *J Anal Toxicol.* 20 (1996) 369-378.
- [11] H.N. Bockbrader, D. Wesche, R. Miller, S. Chapel, N. Janiczek, P. Burger, A comparison of the pharmacokinetics and pharmacodynamics of pregabalin and gabapentin, *Clin Pharmacokinet.* 49 (2010) 661-669.
- [12] R.P. Mattick, C. Been, J. Kimber, M. Davoli, Buprenorphine maintenance versus placebo or methadone maintenance for opioid dependence, *Cochrane Database Syst Rev.* (2014).
- [13] A. Elkader, B. Sproule, Buprenorphine: Clinical Pharmacokinetics in the Treatment of Opioid Dependence, *Clin Pharmacokinet.* 44 (2005) 661-680.
- [14] R. Jagsch, W. Gombas, S. Schindler, H. Eder, D. Moody, G. Fischer, Opioid plasma concentrations in methadone-and buprenorphine-maintained patients, *Addict Biol.* 10 (2005) 365-371.
- [15] D. Brewster, M.J. Humphrey, M.A. McLeavy, Biliary excretion, metabolism and enterohepatic circulation of buprenorphine. *Xenobiotica.* 11 (1981) 189-196.

- [16] E.J. Cone, C.W. Gorodetzky, D. Yousefnejad, W.F. Buchwald, R.E. Johnson, The metabolism and excretion of buprenorphine in humans. *Drug Metab Dispos.* 12 (1984) 577-581.
- [17] M. Ohtani, H. Kotaki, Y. Sawada, T. Iga, Comparative analysis of buprenorphine- and norbuprenorphine-induced analgesic effects based on pharmacokinetic-pharmacodynamic modeling. *J Pharmacol Exp Ther.* 272 (1995) 505-510.
- [18] K. Kobayashi, T. Yamamoto, K. Chiba, M. Tani, N. Shimada, T. Ishizaki, et al., Human buprenorphine N-dealkylation is catalyzed by cytochrome P450 3A4. *Drug Metab Dispos.* 26 (1998) 818-821.
- [19] S.L. Walsh, K.L. Preston, M.L. Stitzer, E.J. Cone, G.E. Bigelow, Clinical pharmacology of buprenorphine: ceiling effects at high doses. *Clin Pharmacol Ther.* 55 (1994) 569-580.
- [20] S.L. Walsh, K.L. Preston, G.E. Bigelow, M.L. Stitzer, Acute administration of buprenorphine in humans: partial agonist and blockade effects. *J Pharmacol Exp Ther.* 274 (1995) 361-372.
- [21] A. Umbricht, M.A. Huestis, E.J. Cone, K.L. Preston, Effects of high-dose intravenous buprenorphine in experienced opioid abusers, *J Clin Psychopharmacol.* 24 (2004) 479-487.
- [22] M. Fatseas, M. Auriacombe, Why buprenorphine is so successful in treating opiate addiction in France, *Curr Psychiatry Rep.* 9 (2007) 358-364.
- [23] J.M. Soeffing, L.D. Martin, M.I. Fingerhood, D.R. Jasinski, D.A. Rastegar, Buprenorphine maintenance treatment in a primary care setting: Outcomes at 1 year, *J Subst Abuse Treat.* 37 (2009) 426-430.
- [24] P. Karvonen, Heroinistien Benedictus-kolmoishoito, *Yhteiskuntapolitiikka.* 63 (1998) 163-179.
- [25] P. Hakkarainen, C. Tigerstedt, Korvaushoidon läpimurto Suomessa [The breakthrough of Finnish substitution treatment (in Finnish, English summary)], *Yhteiskuntapolitiikka.* 70 (2005) 143-154.
- [26] EMCDDA, Drug situation - Finland 2009. National Report to the EMCDDA, (2009).
- [27] K.W. Simonsen, P.T. Normann, G. Ceder, E. Vuori, S. Thordardottir, G. Thelander, et al., Fatal poisoning in drug addicts in the Nordic countries in 2007, *Forensic Sci Int.* 207 (2011) 170-176.
- [28] U. Tacke, Abuse of buprenorphine by intravenous injection—the French connection, *Addiction.* 97 (2002) 1355-1355.
- [29] D.S. Harris, R.T. Jones, S. Welm, R.A. Upton, E. Lin, J. Mendelson, Buprenorphine and naloxone co-administration in opiate-dependent patients stabilized on sublingual buprenorphine, *Drug Alcohol Depend.* 61 (2000) 85-94.
- [30] G.M. Robinson, P.D. Dukes, B.J. Robinson, R.R. Cooke, G.N. Mahoney, The misuse of buprenorphine and a buprenorphine-naloxone combination in Wellington, New Zealand, *Drug Alcohol Depend.* 33 (1993) 81-86.
- [31] H. Alho, D. Sinclair, E. Vuori, A. Holopainen, Abuse liability of buprenorphine–naloxone tablets in untreated IV drug users, *Drug Alcohol Depend.* 88 (2007) 75-78.
- [32] K. Simojoki, H. Vormaa, H. Alho, A retrospective evaluation of patients switched from buprenorphine (Subutex) to the buprenorphine/naloxone combination (Suboxone). *Subst Abuse Treat Prev Policy.* 3 (2008) 16.

- [33] R.D. Bruce, S. Govindasamy, L. Sylla, A. Kamarulzaman, F.L. Altice, Lack of reduction in buprenorphine injection after introduction of co-formulated buprenorphine/naloxone to the Malaysian market, *Am J Drug Alcohol Abuse*. 35 (2009) 68-72.
- [34] B. Larance, L. Degenhardt, N. Lintzeris, J. Bell, A. Winstock, P. Dietze, et al., Post-marketing surveillance of buprenorphine-naloxone in Australia: Diversion, injection and adherence with supervised dosing, *Drug Alcohol Depend*. 118 (2011) 265-273.
- [35] C. Johanson, C.L. Arfken, S. di Menza, C.R. Schuster, Diversion and abuse of buprenorphine: Findings from national surveys of treatment patients and physicians, *Drug Alcohol Depend*. 120 (2012) 190-195.
- [36] K. Simojoki, P. Lillsunde, N. Lintzeris, H. Alho, Bioavailability of Buprenorphine from crushed and whole buprenorphine (Subutex) tablets, *Eur Addict Res*. 16 (2010) 85-90.
- [37] N. Lintzeris, S.Y. Leung, A.J. Dunlop, B. Larance, N. White, G.R. Rivas, et al., A randomised controlled trial of sublingual buprenorphine-naloxone film versus tablets in the management of opioid dependence, *Drug Alcohol Depend*. 131 (2013) 119-126.
- [38] B. Larance, N. Lintzeris, R. Ali, P. Dietze, R. Mattick, R. Jenkinson, et al., The diversion and injection of a buprenorphine-naloxone soluble film formulation, *Drug Alcohol Depend*. 136 (2014) 21-27.
- [39] E.J. Lavonas, S.G. Severtson, E.M. Martinez, B. Bucher-Bartelson, M.C. Le Lait, J.L. Green, et al., Abuse and diversion of buprenorphine sublingual tablets and film, *J Subst Abuse Treat*. 47 (2014) 27-34.
- [40] H. Uosukainen, H. Pentikäinen, U. Tacke, The effect of an electronic medicine dispenser on diversion of buprenorphine-naloxone—experience from a medium-sized Finnish city, *J Subst Abuse Treat*. 45 (2013) 143-147.
- [41] W. Ling, P. Casadonte, G. Bigelow, K.M. Kampman, A. Patkar, G.L. Bailey, et al., Buprenorphine implants for treatment of opioid dependence: a randomized controlled trial, *JAMA*. 304 (2010) 1576-1583.
- [42] R.N. Rosenthal, W. Ling, P. Casadonte, F. Vocci, G.L. Bailey, K. Kampman, et al., Buprenorphine implants for treatment of opioid dependence: randomized comparison to placebo and sublingual buprenorphine/naloxone, *Addiction*. 108 (2013) 2141-2149.
- [43] P.J. Wiffen, S. Derry, R.A. Moore, D. Aldington, P. Cole, A.S. Rice, et al., Antiepileptic drugs for neuropathic pain and fibromyalgia - an overview of Cochrane reviews, *Cochrane Database Syst Rev*. 11 (2013) CD010567.
- [44] W. Häuser, B. Walitt, M.A. Fitzcharles, C. Sommer, Review of pharmacological therapies in fibromyalgia syndrome, *Arthritis Res Ther*. 16 (2014) 201.
- [45] J.E. Frampton, Pregabalin: a review of its use in adults with generalized anxiety disorder, *CNS Drugs*. 28 (2014) 835-854.
- [46] R.P. Allen, C. Chen, D. García-Borreguero, O. Polo, S. DuBrava, J. Miceli, et al., Comparison of pregabalin with pramipexole for restless legs syndrome, *N Engl J Med*. 370 (2014) 621-631.
- [47] R. Guglielmo, G. Martinotti, M. Clerici, L. Janiri, Pregabalin for alcohol dependence: a critical review of the literature, *Adv Ther*. 29 (2012) 947-957.

- [48] T. Keränen, E. Pöntinen, K. Laitinen, Pregabaliinin teho myyntiluvan ulkopuolisissa käyttöaiheissa, *Finnish Med J.* 67 (2012) 2563-2565.
- [49] N. Attal, G. Cruccu, R. Baron, M. Haanpää, P. Hansson, T.S. Jensen, et al., EFNS guidelines on the pharmacological treatment of neuropathic pain: 2010 revision, *Eur J Neurol.* 17 (2010) 1113-1123.
- [50] S. Joukanen, Pregabaliinin väärinkäyttö on lisääntynyt, *Finnish Med J.* 66 (2011) 756-759.
- [51] E. Vuori, I. Ojanperä, J. Nokua, R.L. Ojansivu, Oikeuskemiallisesti todetut myrkytyskuolemat Suomessa vuosina 2005–2007 [Fatal poisonings in Finland during 2005–2007 (in Finnish, English summary)], *Finnish Med J.* 64 (2009) 3187-3195.
- [52] A. Gatti, A.F. Sabato, R. Occhioni, G. Colini Baldeschi, C. Reale, Controlled-release oxycodone and pregabalin in the treatment of neuropathic pain: results of a multicenter Italian study, *Eur Neurol.* 61 (2009) 129-137.
- [53] Y. Vorobeychik, V. Gordin, J. Mao, L. Chen, Combination therapy for neuropathic pain: a review of current evidence, *CNS Drugs.* 25 (2011) 1023-1034.
- [54] M.C. Garassino, S. Piva, N. La Verde, I. Spagnoletti, V. Iorno, C. Carbone, et al., Randomised phase II trial (NCT00637975) evaluating activity and toxicity of two different escalating strategies for pregabalin and oxycodone combination therapy for neuropathic pain in cancer patients, *PLoS One.* 8 (2013) e59981.
- [55] S. Lottner-Nau, B. Övgüer, L.D. Paul, M. Graw, H. Sachs, G. Roider, Abuse of pregabalin – results of the postmortem toxicology from 2010 to 2012, *Toxichem Krimtech.* 80 (2013) 339-342.
- [56] M. Grosshans, T. Lemenager, C. Vollmert, N. Kämmerer, R. Screiner, J. Mutschler, et al., Pregabalin abuse among opiate addicted patients, *Eur J Clin Pharmacol.* 69 (2013) 2021-2025.
- [57] C.R. Baird, P. Fox, L.A. Colvin, Gabapentinoid abuse in order to potentiate the effect of methadone: a survey among substance misusers, *Eur Addict Res.* 20 (2014) 115-118.
- [58] R.R. Reeves, M.E. Ladner, Potentiation of the effect of buprenorphine/naloxone with gabapentin or quetiapine, *Am J Psychiatry.* 171 (2014) 691.
- [59] A.K. Jönsson, C. Söderberg, K.A. Espnes, J. Ahlner, A. Eriksson, M. Reis, et al., Sedative and hypnotic drugs – fatal and non-fatal reference blood concentrations, *Forensic Sci Int.* 236 (2014) 138-145.
- [60] S. Niemelä, A. Mikkonen, Tunnista lääkkeiden väärinkäyttäjät ja päihdekäyttöön tulleet lääkkeet [How to recognize drug abusers and the medicines being used (in Finnish, English summary)], *Finnish Med J.* 69 (2014) 624-627.
- [61] J.H. Jaffe, R. Bloor, I. Crome, M. Carr, F. Alam, A. Simmons, et al., A postmarketing study of relative abuse liability of hypnotic sedative drugs, *Addiction.* 99 (2004) 165-173.
- [62] Bentsodiatsepiinien määrääminen [Prescription of benzodiazepines], Valvira [The National Supervisory Authority for Welfare and Health], http://www.valvira.fi/ohjaus_ja_valvonta/terveydenhuolto/laakehoito/bentsodiatsepiinien_maaraaminen_2, accessed on May 15, 2014.
- [63] P. Kriikku, L. Wilhelm, J. Rintatalo, J. Hurme, J. Kramer, I. Ojanperä, Phenazepam abuse in Finland: findings from apprehended drivers, post-mortem cases and police confiscations, *Forensic Sci Int.* 220 (2012) 111-117.

- [64] J.M. Corkery, F. Schifano, A.H. Ghodse, Phenazepam abuse in the UK: an emerging problem causing serious adverse health problems, including death, *Hum Psychopharmacol.* 27 (2012) 254-261.
- [65] J.D. Jones, S. Mogali, S.D. Comer, Polydrug abuse: a review of opioid and benzodiazepine combination use, *Drug Alcohol Depend.* 125 (2012) 8-18.
- [66] E. Lavie, M. Fatseas, C. Denis, M. Auriacombe, Benzodiazepine use among opiate-dependent subjects in buprenorphine maintenance treatment: correlates of use, abuse and dependence. *Drug Alcohol Depend.* 99 (2009) 338-344.
- [67] M. Vogel, B. Knöpfli, O. Schmid, M. Prica, J. Strasser, L. Prieto, et al., Treatment or "high": benzodiazepine use in patients on injectable heroin or oral opioids, *Addict Behav.* 38 (2013) 2477-2484.
- [68] P.K. Heikman, I.A. Ojanperä, Inadequate dose of opioid-agonist medication is related to misuse of benzodiazepine, *Addict Disord Their Treatment.* 8 (2009) 145-153.
- [69] Z. Schuman-Olivier, B.B. Hoepfner, R.D. Weiss, J. Borodovsky, H.J. Shaffer, M.J. Albanese, Benzodiazepine use during buprenorphine treatment for opioid dependence: clinical and safety outcomes, *Drug Alcohol Depend.* 132 (2013) 580-586.
- [70] N. Lintzeris, S. Nielsen, Benzodiazepines, methadone and buprenorphine: interactions and clinical management, *Am J Addict.* 19 (2010) 59-72.
- [71] M. Jann, W.K. Kennedy, G. Lopez, Benzodiazepines: a major component in unintentional prescription drug overdoses with opioid analgesics, *J Pharm Pract.* 27 (2014) 5-16.
- [72] S.C. Lee, W. Klein-Schwartz, S. Doyon, C. Welsh, Comparison of toxicity associated with nonmedical use of benzodiazepines with buprenorphine or methadone, *Drug Alcohol Depend.* 138 (2014) 118-123.
- [73] J. Højsted, O. Ekholm, G.P. Kurita, K. Juel, P. Sjøgren, Addictive behaviors related to opioid use for chronic pain: a population-based study, *Pain.* 154 (2013) 2677-2683.
- [74] E. Vuori, I. Ojanperä, J. Nokua, R. Ojansivu, Oikeuskemiallisesti todetut myrkytyskuolemat Suomessa 2000 ja 2001, *Finnish Med J.* 58 (2003) 3403-3407.
- [75] E. Vuori, I. Ojanperä, J. Nokua, R. Ojansivu, Oikeuskemiallisesti todetut myrkytyskuolemat Suomessa 2002-2004, *Finnish Med J.* 61 (2006) 2339-2344.
- [76] J. Boyd, Treatment of illicit opioid and γ -hydroxybutyrate overdose by Helsinki emergency medical services, University of Helsinki, Helsinki, 2011.
- [77] L. Degenhardt, C. Bucello, B. Mathers, C. Briegleb, H. Ali, M. Hickman, et al., Mortality among regular or dependent users of heroin and other opioids: a systematic review and meta-analysis of cohort studies, *Addiction.* 106 (2010) 32-51.
- [78] I.N. Onyeka, C.M. Beynon, M.L. Hannila, J. Tiihonen, J. Föhr, P. Tuomola, et al., Patterns and 14-year trends in mortality among illicit drug users in Finland: the HUUTI study, *Int J Drug Policy.* 25 (2014) 1047-1053.
- [79] P. Kintz, P. Marquet, Buprenorphine therapy of opiate addiction, in: Karch S.B. (Ed.), *Forensic Science and Medicine*, Humana Press, Totowa, New Jersey, 2002, pp. 109-117.
- [80] P. Kintz, A new series of 13 buprenorphine-related deaths. *Clin Biochem.* 35 (2002) 513-516.
- [81] P. Kintz, Deaths involving buprenorphine: a compendium of French cases, *Forensic Sci Int.* 121 (2001) 65-69.

- [82] S.H. Lai, Y.J. Yao, D.S.T. Lo, A survey of buprenorphine related deaths in Singapore, *Forensic Sci Int.* 162 (2006) 80-86.
- [83] J.J.J. Kuhlman, R. McCaulley, T.J. Valouch, G.S. Behonick, Fentanyl use, misuse, and abuse: a summary of 23 postmortem cases, *J Anal Toxicol.* 27 (2003) 499-504.
- [84] S. Darke, Opioid overdose and the power of old myths: What we thought we knew, what we do know and why it matters, *Drug Alcohol Rev.* 33 (2014) 109-114.
- [85] S. Darke, M. Farrell, Would legalizing illicit opioids reduce overdose fatalities? Implications from a natural experiment, *Addiction.* 109 (2014) 1237-1242.
- [86] J.M. White, R.J. Irvine, Mechanisms of fatal opioid overdose, *Addiction.* 94 (1999) 961-972.
- [87] O. Ferrant, F. Papin, B. Clin, C. Lacroix, E. Saussereau, J. Remoué, et al., Fatal poisoning due to snorting buprenorphine and alcohol consumption, *Forensic Sci Int.* 204 (2011) e8-e11.
- [88] A. Pelissier-Alicot, C. Sastre, V. Baillif-Couniou, J. Gaulier, P. Kintz, E. Kuhlmann, et al., Buprenorphine-related deaths: unusual forensic situations, *Int J Legal Med.* 124 (2010) 647-651.
- [89] T. Launiainen, I. Ojanperä, Drug concentrations in post-mortem femoral blood compared with therapeutic concentrations in plasma, *Drug Test Anal.* 6 (2014) 308-316.
- [90] P. Madadi, D. Hildebrandt, A.E. Lauwers, G. Koren, Characteristics of opioid-users whose death was related to opioid-toxicity: a population-based study in Ontario, Canada, *PLoS One.* 8 (2013) e60600.
- [91] J.-P. Bernard, I. Havnes, L. Slørdal, H. Waal, J. Mørland, H.Z. Khiabani, Methadone-related deaths in Norway, *Forensic Sci Int.* 224 (2013) 111-116.
- [92] T. Launiainen, U. Broms, K. Kesitalo-Vuokko, J. Pitkaniemi, A. Pelander, J. Kaprio, et al., Nicotine, alcohol, and drug findings in young adults in a population-based postmortem database, *Nicotine Tob Res.* 13 (2011) 763-771.
- [93] A.L. Pélissier-Alicot, J.M. Gaulier, P. Champsaur, P. Marquet, Mechanisms underlying postmortem redistribution of drugs: a review, *J Anal Toxicol.* 27 (2003) 533-544.
- [94] R.E. Ferner, Post-mortem clinical pharmacology, *Br J Clin Pharmacol.* 66 (2008) 430-443.
- [95] I. Costa, A. Oliveira, P. Guedes de Pinho, H.M. Teixeira, R. Moreira, F. Carvalho, et al., Postmortem redistribution of tramadol and O-desmethyiltramadol, *J Anal Toxicol.* 37 (2013) 670-675.
- [96] I.M. McIntyre, D.T. Anderson, Postmortem Fentanyl Concentrations: A Review, *J Forensic Res.* 3 (2012) 157.
- [97] S.S. Tolliver, W.L. Hearn, K.G. Furton, Evaluating the relationship between postmortem and antemortem morphine and codeine concentrations in whole blood, *J Anal Toxicol.* 34 (2010) 491-497.
- [98] K.N. Olson, K. Luckenbill, J. Thompson, O. Middleton, R. Geiselhart, K.M. Mills, et al., Postmortem redistribution of fentanyl in blood, *Am J Clin Pathol.* 133 (2010) 447-453.
- [99] I.M. McIntyre, R.D. Gary, J. Estrada, C.L. Nelson, Antemortem and postmortem fentanyl concentrations: a case report, *Int J Legal Med.* 128 (2014) 65-67.

- [100] D. Gerostamoulos, J. Beyer, V. Staikos, P. Tayler, N. Woodford, O.H. Drummer, The effect of the postmortem interval on the redistribution of drugs: a comparison of mortuary admission and autopsy blood specimens, *Forensic Sci Med Pathol.* 8 (2012) 373-379.
- [101] Y. Gasche, Y. Daali, M. Fathi, A. Chiappe, S. Cottini, P. Dayer, et al., Codeine Intoxication Associated with Ultrarapid CYP2D6 Metabolism, *N Engl J Med.* 351 (2004) 2827-2831.
- [102] J. Kirchheiner, H. Schmidt, M. Tzvetkov, J.T. Keulen, J. Lötsch, I. Roots, et al., Pharmacokinetics of codeine and its metabolite morphine in ultra-rapid metabolizers due to CYP2D6 duplication, *Pharmacogenomics J.* 7 (2007) 257-265.
- [103] J. Kirchheiner, J.T. Keulen, S. Bauer, I. Roots, J. Brockmöller, Effects of the CYP2D6 gene duplication on the pharmacokinetics and pharmacodynamics of tramadol, *J Clin Psychopharmacol.* 28 (2008) 78-83.
- [104] H. Bunten, W.J. Liang, D. Pounder, C. Seneviratne, M.D. Osselson, CYP2B6 and OPRM1 gene variations predict methadone-related deaths, *Addict Biol.* 16 (2011) 142-144.
- [105] T. Seldén, M. Roman, H. Druid, R. Kronstrand, LC-MS-MS analysis of buprenorphine and norbuprenorphine in whole blood from suspected drug users, *Forensic Sci Int.* 209 (2011) 113-119.
- [106] A.W. Jones, A. Holmgren, J. Ahlner, Blood methadone concentrations in living and deceased persons: variations over time, subject demographics, and relevance of coingested drugs, *J Anal Toxicol.* 36 (2012) 12-18.
- [107] A.J. Braga, K. Chidley, Self-poisoning with lamotrigine and pregabalin, *Anaesthesia.* 62 (2007) 524-527.
- [108] D.M. Wood, D.J. Berry, G. Glover, J. Eastwood, P.I. Dargan, Significant pregabalin toxicity managed with supportive care alone, *J Med Toxicol.* 6 (2010) 435-437.
- [109] O.H. Drummer, Postmortem toxicology of drugs of abuse, *Forensic Sci.Int.* 142 (2004) 101-113.
- [110] M.C. Milone, Laboratory testing for prescription opioids, *J Med Toxicol.* 8 (2012) 408-416.
- [111] J.P. Bernard, M.S. Opdal, R. Karinen, J. Mørland, H.Z. Khiabani, Relationship between methadone and EDDP (2-ethylidene-1,5-dimethyl-3,3-diphenylpyrrolidine) in urine samples from Norwegian prisons, *Eur J Clin Pharmacol.* 63 (2007) 777-782.
- [112] M.E. Larson, T.M. Richards, Quantification of a methadone metabolite (EDDP) in urine: assessment of compliance, *Clin Med Res.* 7 (2009) 134-141.
- [113] S.M. Smith, R.C. Dart, N.P. Katz, F. Paillard, E.H. Adams, S.D. Comer, et al., Classification and definition of misuse, abuse, and related events in clinical trials: ACTION systematic review and recommendations, *Pain.* 154 (2013) 2287-2296.
- [114] E. Souton, C. Cohier, L. Chevillard, P. Risède, B. Mégarbane, Investigation of respiratory effects of norbuprenorphine and their modulation in rat to define its contribution to buprenorphine toxicity, *Clin Toxicol.* 52 (2014) 356-357.
- [115] C. Cohier, L. Chevillard, P. Risède, O. Roussel, B. Mégarbane, Respiratory effects of buprenorphine/naloxone alone and in combination with diazepam in naive and tolerant rats, *Toxicol Lett.* 228 (2014) 75-84.
- [116] J.E. Sprague, M. Leifheit, J. Selken, M.M. Milks, D.H. Kinder, D.E. Nichols, In vivo microdialysis and conditioned place preference studies in rats are consistent with abuse potential of tramadol, *Synapse.* 43 (2002) 118-121.

- [117] K. Oppek, G. Koller, A. Zwergal, O. Pogarell, Intravenous Administration and Abuse of Bupropion: A Case Report and a Review of the Literature, *J Addict Med.* 8 (2014) 290-293.
- [118] K. Karjalainen, P. Hakkarainen, Lääkkeiden väärinkäyttö 2000-luvun Suomessa. Esiintyvyys, käyttäjäryhmät ja käyttötarkoitukset [Non-medical use of prescription drugs in Finland: a population-based survey (in Finnish, English summary)], *Yhteiskuntapolitiikka*. 78 (2013) 498-508.
- [119] L. Metso, T. Winter, P. Hakkarainen, Suomalaisten huumeiden käyttö ja huumeasenteet – Huumeaiheiset väestökyselyt Suomessa 1992–2010 [Drug use and drug attitudes among Finns – Drug-related population surveys in Finland 1992–2010 (in Finnish, English summary)], National Institute for Health and Welfare (THL), Helsinki, Finland, 2011.
- [120] P. Hakkarainen, L. Metso, M. Salasuo, Hampuikäpolvi, sekakäyttö ja doping – Vuoden 2010 huumeikyselyn tulokset [The hemp generation, mixed use and doping – results from the 2010 Drug Survey (in Finnish, English summary)], *Yhteiskuntapolitiikka*. 76 (2011) 396-413.
- [121] T. Tammi, T. Pitkänen, J. Perälä, Stadin nistit – huono-osaisten helsinkiläisten huumeidenkäyttäjien päihteet sekä niiden käyttötavat ja hankinta [Disadvantaged drug users in Helsinki: what drugs do they use, how do they use them and how do they get them (in Finnish, English summary)], *Yhteiskuntapolitiikka*. 76 (2011) 45-54.
- [122] M. Gahr, R.W. Freudenmann, C. Hiemke, M.A. Kölle, C. Schönfeldt-Lecuona, Abuse of methylphenidate in Germany: data from spontaneous reports of adverse drug reactions, *Psychiatry Res.* 215 (2014) 252-254.
- [123] J.L. Green, E.M. Martinez, S. Walcher, L. Somaini, G. Deruvo, H. Desel, et al., 180. Prescription opioid misuse in Europe: From opioid treatment programs to Poison Centres, *Clin Toxicol.* 52 (2014) 372-372.
- [124] E. Hirvonen, E. Annala, M. From, Finnish Customs Investigation Report 2011, Customs Investigation Service, 2012.
- [125] P. Kriikku, L. Wilhelm, J. Rintatalo, J. Hurme, J. Kramer, I. Ojanperä, Pregabalin serum levels in apprehended drivers, *Forensic Sci Int.* 243 (2014) 112-116.
- [126] E. Zuccato, C. Chiabrando, S. Castiglioni, R. Bagnati, R. Fanelli, Estimating Community Drug Abuse by Wastewater Analysis, *Environ Health Perspect.* 116 (2008) 1027-1032.
- [127] E. Vuori, M. Happonen, M. Gergov, T. Nenonen, A. Järvinen, R.A. Ketola, et al., Wastewater analysis reveals regional variability in exposure to abused drugs and opioids in Finland, *Sci Total Environ.* 487 (2014) 688-695.
- [128] M. Chary, N. Genes, A. McKenzie, A.F. Manini, Leveraging social networks for toxicovigilance, *J Med Toxicol.* 9 (2013) 184-191.
- [129] M. Chary, N. Genes, A.F. Manini, Using Twitter to measure underage alcohol usage, *Clin Toxicol.* 52 (2014) 304-304.
- [130] F. Schifano, S. D'Offizi, M. Piccione, O. Corazza, P. Deluca, Z. Davey, et al., Is there a recreational misuse potential for pregabalin? Analysis of anecdotal online reports in comparison with related gabapentin and clonazepam data. *Psychother Psychosom.* 80 (2011) 118-122.
- [131] P. Deluca, Z. Davey, O. Corazza, L. Di Furia, M. Farre, L.H. Flesland, et al., Identifying emerging trends in recreational drug use; outcomes from the Psychonaut

- Web Mapping Project, *Prog Neuropsychopharmacol Biol Psychiatry*. 39 (2012) 221-226.
- [132] B.N. Cochran, A. Flentje, N.C. Heck, J. Van Den Bos, D. Perlman, J. Torres, et al., Factors predicting development of opioid use disorders among individuals who receive an initial opioid prescription: Mathematical modeling using a database of commercially-insured individuals, *Drug Alcohol Depend.* 138 (2014) 202-208.
- [133] D. Li, H. Zhao, H.R. Kranzler, M.D. Li, K.P. Jensen, T. Zayats, et al., Genome-Wide Association Study of Copy Number Variations (CNVs) with Opioid Dependence, *Neuropsychopharmacology*. 40 (2015) 1016-1026.
- [134] P. Partanen, P. Hakkarainen, A. Hankilanoja, K. Kuussaari, S. Rönkä, M. Salminen, et al., Amfetamiinien ja opiaattien ongelmakäytön yleisyys Suomessa 2005, *Yhteiskuntapolitiikka*. 72 (2007) 553-561.
- [135] J. Ollgren, M. Forsell, V. Varjonen, H. Alho, H. Brummer-Korvenkontio, H. Kainulainen, et al., Amfetamiinien ja opioidien ongelmakäytön yleisyys Suomessa 2012 [The prevalence of amphetamine and opioid abuse in Finland in 2012 (in Finnish, English summary)], *Yhteiskuntapolitiikka*. 79 (2014) 498-508.
- [136] M. Aalto, J. Halme, J.P. Visapää, M. Salaspuro, Buprenorphine misuse in Finland, *Subst Use Misuse*. 42 (2007) 1027-1028.
- [137] K. Malin, A. Holopainen, J. Tourunen, "Mä käytän subua, että mä pysyn terveenä ja pystyn toimimaan": käyttäjän kokemuksia ja näkemyksiä buprenorfiinin käytöstä, *Yhteiskuntapolitiikka*. 71 (2006) 297-306.
- [138] T. Lintonen, A. Konu, S. Rönkä, E. Kotovirta, Drugs foresight 2020: a Delphi expert panel study, *Subst Abuse Treat Prev Policy*. 9 (2014).
- [139] K.W. Simonsen, H.M. Edvardsen, G. Thelander, I. Ojanperä, S. Thordardottir, L.V. Andersen, et al., Fatal poisoning in drug addicts in the Nordic countries in 2012, *Forensic Sci Int*. 248C (2015) 178-180.
- [140] M. Piispa, Eivät huumeet yksin tapa – huumeisiin liittyvät kuolemat Suomessa 2007 [Drug-related deaths in Finland 2007 (in Finnish, English summary)], *Yhteiskuntapolitiikka*. 76 (2011) 169-180.
- [141] I.N. Onyeka, H. Uosukainen, M.J. Korhonen, C. Beynon, J.S. Bell, K. Ronkainen, et al., Sociodemographic characteristics and drug abuse patterns of treatment-seeking illicit drug abusers in Finland, 1997-2008: the Huuti study, *J Addict Dis*. 31 (2012) 350-362.
- [142] J.A. Banken, H. Foster, Dextromethorphan. An emerging drug of abuse, *An N Y Acad Sci*. 1139 (2008) 402-411.
- [143] R.R. Reeves, M.E. Ladner, Additional evidence of the abuse potential of bupropion, *J Clin Psychopharmacol*. 33 (2013) 584-585.
- [144] C.J. Morgan, H.V. Curran, Independent Scientific Committee on Drugs, Ketamine use: a review, *Addiction*. 107 (2012) 27-38.
- [145] A. Roussin, J.L. Montastruc, M. Lapeyre-Mestre, Pharmacological and clinical evidences on the potential for abuse and dependence of propofol: a review of the literature, *Fundam Clin Pharmacol*. 21 (2007) 459-466.
- [146] R.A. Sansone, L.A. Sansone, Is seroquel developing an illicit reputation for misuse/abuse? *Psychiatry (Edgmont)*. 7 (2010) 13-16.
- [147] W. Klein-Schwartz, E.K. Schwartz, B.D. Anderson, Evaluation of quetiapine abuse and misuse reported to poison centers, *J Addict Med*. 8 (2014) 195-198.
- [148] R.R. Reeves, R.S. Burke, S. Kose, Carisoprodol: update on abuse potential and legal status, *South Med J*. 105 (2012) 619-623.

- [149] International Classification of Diseases (ICD-10), 10 th ed., World Health Organization, 2007, <http://www.who.int/classifications/apps/icd/icd10online/>, accessed November 28, 2014.
- [150] Huumeongelmaisen käypä hoito [Treatment of drug abuse (online). Current Care Guidelines (in Finnish, English summary)], 2012, www.kaypahoito.fi, accessed on November 11, 2014.
- [151] EMCDDA, European drug report. Trends and developments, EMCDDA 2014.
- [152] A. Partanen, H. Vormo, H. Alho, A. Leppo, Opioidiriippuvuuden lääkkeellinen vieroitus- ja korvaushoito Suomessa [Detoxification and substitution in the treatment of opioid addicts in Finland in 2011: Is treatment becoming more varied? (in Finnish, English summary), *Finnish Med J.* 69 (2014) 481-486.
- [153] Act on Welfare for Substance Abusers (41/1986), Ministry of Social Affairs and Health, Finland 1986.
- [154] Decree of the Ministry of Social Affairs and Health on the detoxification and substitution treatment of opioid addicts with certain medicinal products (33/2008), Ministry of Social Affairs and Health, Finland, <http://www.finlex.fi/en/laki/kaannokset/2008/en20080033.pdf>, accessed on November 6, 2014.
- [155] H. Uosukainen, J.S. Bell, K. Laitinen, U. Tacke, J. Ilomäki, J.H. Turunen, First insights into community pharmacy based buprenorphine-naloxone dispensing in Finland, *Int J Drug Policy.* 24 (2013) 492-497.
- [156] M. Aalto, J. Visapää, J.T. Halme, C. Fabritius, M. Salaspuro, Effectiveness of buprenorphine maintenance treatment as compared to a syringe exchange program among buprenorphine misusing opioid-dependent patients, *Nord J Psychiatry.* 65 (2011) 238-243.
- [157] CMDh endorses suspension of methadone oral solutions containing high molecular weight povidone, European Medicines Agency, 2014, http://www.ema.europa.eu/docs/en_GB/document_library/Press_release/2014/07/WC500170053.pdf, accessed on December 5, 2014.
- [158] S. Okie, A flood of opioids, a rising tide of deaths, *N Engl J Med.* 18 (2010) 1981-1985.
- [159] R. Nicholas, N. Lee, A. Roche, Pharmaceutical Drug Misuse in Australia: Complex problems, balanced responses, National Centre for Education and Training on Addiction (NCETA), Flinders University, Adelaide, 2011.
- [160] J.E. Couto, M.C. Romney, H.L. Leider, S. Sharma, N.I. Goldfarb, High rates of inappropriate drug use in the chronic pain population, *Popul Health Manag.* 12 (2009) 185-190.
- [161] Finnish Statistics on Medicines 2000, Finnish Medicines Agency FIMEA and Social Insurance Institution, Helsinki, 2001.
- [162] Finnish Statistics on Medicines 2004, Finnish Medicines Agency FIMEA and Social Insurance Institution, Helsinki, 2005.
- [163] Finnish Statistics on Medicines 2008, Finnish Medicines Agency FIMEA and Social Insurance Institution, Helsinki, 2009.
- [164] Finnish Statistics on Medicines 2011, Finnish Medicines Agency FIMEA and Social Insurance Institution, Helsinki, 2012.
- [165] L. Alexander, R.O. Mannion, B. Weingarten, R.J. Fanelli, G.L. Stiles, Development and impact of prescription opioid abuse deterrent formulation technologies, *Drug Alcohol Depend.* 138 (2014) 1-6.

- [166] T.A. Cassidy, P. DasMahapatra, R.A. Black, M.S. Wieman, S.F. Butler, Changes in prevalence of prescription opioid abuse after introduction of an abuse-deterrent opioid formulation, *Pain Med.* 15 (2014) 440-451.
- [167] N. Dasgupta, K. Creppage, A. Austin, C. Ringwalt, C. Sanford, S.K. Proescholdbell, Observed transition from opioid analgesic deaths toward heroin, *Drug Alcohol Depend.* 145C (2014) 238-241.
- [168] D. Lee, C. Delcher, M.M. Maldonado-Molina, L.A. Bazydlo, J.R. Thogmartin, B.A. Goldberger, Trends in licit and illicit drug-related deaths in Florida from 2001 to 2012, *Forensic Sci Int.* 245C (2014) 178-186.
- [169] I.A. Dhalla, N. Persaud, D.N. Juurlink, Facing up to the prescription opioid crisis, *BMJ.* 343 (2011) d5142.
- [170] Laki sähköisestä lääkemääräyksestä annetun lain muuttamisesta 251/2014 [Act on amending the act of the electronic prescription (251/2014) (in Finnish)], Ministry of Social Affairs and Health, Finland, <http://www.finlex.fi/fi/laki/alkup/2014/20140251>, accessed on November 16, 2014.
- [171] B.N. Wikner, I. Ohman, T. Seldén, H. Druid, L. Brandt, H. Kieler, Opioid-related mortality and filled prescriptions for buprenorphine and methadone, *Drug Alcohol Rev.* 33 (2014) 491-498.
- [172] A. Pelander, I. Ojanperä, S. Laks, I. Rasanen, E. Vuori, Toxicological screening with formula-based metabolite identification by liquid chromatography/time-of-flight mass spectrometry, *Anal Chem.* 75 (2003) 5710-5718.
- [173] S. Ojanperä, A. Pelander, M. Pelzing, I. Krebs, E. Vuori, I. Ojanperä, Isotopic pattern and accurate mass determination in urine drug screening by liquid chromatography/time-of-flight mass spectrometry, *Rapid Commun Mass Sp.* 20 (2006) 1161-1167.
- [174] I. Ojanperä, I. Rasanen, E. Vuori, Automated quantitative screening for acidic and neutral drugs in whole blood by dual-column capillary gas chromatography. *J Anal Toxicol.* 15 (1991) 204-208.
- [175] I. Rasanen, I. Ojanpera, E. Vuori, Quantitative screening for benzodiazepines in blood by dual-column gas chromatography and comparison of the results with urine immunoassay. *J Anal Toxicol.* 24 (2000) 46-53.
- [176] I. Rasanen, I. Kontinen, J. Nokua, I. Ojanperä, E. Vuori, Precise gas chromatography with retention time locking in comprehensive toxicological screening for drugs in blood, *J Chromatogr B.* 788 (2003) 243-250.
- [177] M. Gergov, P. Nokua, E. Vuori, I. Ojanperä, Simultaneous screening and quantification of 25 opioid drugs in post-mortem blood and urine by liquid chromatography–tandem mass spectrometry, *Forensic Sci Int.* 186 (2009) 36-43.
- [178] T. Seldén, J. Ahlner, H. Druid, R. Kronstrand, Toxicological and pathological findings in a series of buprenorphine related deaths. Possible risk factors for fatal outcome, *Forensic Sci Int.* 220 (2012) 284-290.
- [179] M. Schulz, S. Iwersen-Bergmann, H. Andresen, A. Schmoldt, Therapeutic and toxic blood concentrations of nearly 1,000 drugs and other xenobiotics, *Crit Care.* 16 (2012) R136.
- [180] C. Priez-Barallon, J. Carlier, B. Boyer, M. Benslimi, L. Fanton, C. Mazoyer, et al., Quantification of pregabalin using hydrophilic interaction HPLC-high-resolution MS in postmortem human samples: eighteen case reports, *J Anal Toxicol.* 38 (2014) 143-148.

- [181] M. Salasuo, E. Vuori, M. Piispa, P. Hakkarainen, Suomalainen huumekuolema 2007. Poikkitieteellinen tutkimus oikeuslääketieteellisistä kuolinsyyasiakirjoista, (2009).
- [182] F. Schifano, Misuse and abuse of pregabalin and gabapentin: cause for concern? *CNS Drugs*. 28 (2014) 491-496.
- [183] C.M. Jones, L.J. Paulozzi, K.A. Mack, Alcohol involvement in opioid pain reliever and benzodiazepine drug abuse-related emergency department visits and drug-related deaths – United States, 2010, *MMWR Morb Mortal Wkly Rep*. 63 (2014) 881-885.
- [184] M.J. Hull, M.F. Bierer, D.A. Griggs, W.H. Long, A.L. Nixon, J.G. Flood, Urinary Buprenorphine Concentrations in Patients Treated with Suboxone®; as Determined by Liquid Chromatography-Mass Spectrometry and CEDIA Immunoassay, *J Anal Toxicol*. 32 (2008) 516-521.
- [185] M.A. Yokell, N.D. Zaller, T.C. Green, M. McKenzie, J.D. Rich, Intravenous use of illicit buprenorphine/naloxone to reverse an acute heroin overdose, *J Opioid Manag*. 8 (2012) 63-66.
- [186] S. Iwersen-Bergmann, H. Jungen, H. Andresen-Streichert, A. Müller, S. Elakkary, K. Püschel, et al., Intravenous methadone application as a serious risk factor for an overdose death: methadone-related fatalities in Hamburg from 2007 to 2012, *Int J Legal Med*. 128 (2014) 751-764.
- [187] E. García Quetglas, J.R. Azanza, E. Cardenas, B. Sádaba, M.A. Campanero, Stereoselective pharmacokinetic analysis of tramadol and its main phase I metabolites in healthy subjects after intravenous and oral administration of racemic tramadol, *Biopharm Drug Dispos*. 28 (2007) 19-33.
- [188] R. Parasrampur, R. Vuppugalla, K. Elliott, R. Mehvar, Route-dependent stereoselective pharmacokinetics of tramadol and its active O-demethylated metabolite in rats, *Chirality*. 19 (2007) 190-196.
- [189] P.K. Lilleng, L.I. Mehlum, L. Bachs, I. Morild, Deaths after intravenous misuse of transdermal fentanyl, *J Forensic Sci*. 49 (2004) 1364-1366.
- [190] A.M. Tharp, R.E. Winecker, D.C. Winston, Fatal intravenous fentanyl abuse: four cases involving extraction of fentanyl from transdermal patches, *Am J Forensic Med Pathol*. 25 (2004) 178-181.
- [191] C. Kramer, M. Tawney, A fatal overdose of transdermally administered fentanyl, *J Am Osteopath Assoc*. 98 (1998) 385-386.
- [192] K.L. Woodall, T.L. Martin, B.A. McLellan, Oral abuse of fentanyl patches (Duragesic): seven case reports, *J Forensic Sci*. 53 (2008) 222-225.
- [193] T.L. Martin, K.L. Woodall, B.A. McLellan, Fentanyl-related deaths in Ontario, Canada: toxicological findings and circumstances of death in 112 cases (2002-2004), *J Anal Toxicol*. 30 (2006) 603-610.
- [194] S. Rönkä, K. Karjalainen, E. Vuori, P. Mäkelä, Personally prescribed psychoactive drugs in overdose deaths among drug abusers: A retrospective register study, *Drug Alcohol Rev*. 34 (2015) 82-89.
- [195] K.E. Goeringer, B.K. Logan, G.D. Christian, Identification of tramadol and its metabolites in blood from drug-related deaths and drug-impaired drivers, *J Anal Toxicol*. 21 (1997) 529-537.
- [196] L. Radbruch, S. Grond, K.A. Lehmann, A risk-benefit assessment of tramadol in the management of pain, *Drug Saf*. 15 (1996) 8-29.

- [197] S. Grond, A. Sablotzki, Clinical pharmacology of tramadol, *Clin Pharmacokinet.* 43 (2004) 879-923.
- [198] T.J. Cicero, J.A. Inciardi, E.H. Adams, A. Geller, E.C. Senay, G.E. Woody, et al., Rates of abuse of tramadol remain unchanged with the introduction of new branded and generic products: results of an abuse monitoring system, 1994-2004, *Pharmacoepidemiol Drug Saf.* 14 (2005) 851-859.
- [199] D.H. Epstein, K.L. Preston, D.R. Jasinski, Abuse liability, behavioral pharmacology, and physical-dependence potential of opioids in humans and laboratory animals: lessons from tramadol, *Biol Psychol.* 73 (2006) 90-99.
- [200] L. Radbruch, G. Glaeske, S. Grond, F. Münchberg, N. Scherbaum, E. Storz, et al., Topical review on the abuse and misuse potential of tramadol and tilidine in Germany, *Subst Abuse.* 34 (2013) 313-210.
- [201] J.P. Zacny, Profiling the subjective, psychomotor, and physiological effects of tramadol in recreational drug users, *Drug Alcohol Depend.* 80 (2005) 273-278.
- [202] S. Babalonis, M.R. Lofwall, P.A. Nuzzo, A.J. Siegel, S.L. Walsh, Abuse liability and reinforcing efficacy of oral tramadol in humans, *Drug Alcohol Depend.* 129 (2013) 116-124.
- [203] K.K. Rigg, G.E. Ibañez, Motivations for non-medical prescription drug use: a mixed methods analysis, *J Subst Abuse Treat.* 39 (2010) 236-247.
- [204] S.E. McCabe, J.A. Cranford, Motivational subtypes of nonmedical use of prescription medications: results from a national study, *J Adolesc Health.* 51 (2012) 445-452.
- [205] J. Nevantaus, K. Simojoki, K. Hamunen, T. Heiskanen, E. Kalso, Opioidit pitkääikäisen kivun hoidossa [Opioids in the treatment of chronic pain (in Finnish, English summary)], *Finnish Med J.* 50-52 (2013) 3329-3335.
- [206] J.L. Pilgrim, S.P. Yafistham, S. Gaya, E. Saar, O.H. Drummer, An update on oxycodone: lessons for death investigators in Australia, *Forensic Sci Med Pathol.* 11 (2015) 3-12.
- [207] H. Jungen, H. Andresen-Streichert, A. Müller, S. Iwersen-Bergmann, Disaccharides in urine samples as markers of intravenous abuse of methadone and buprenorphine, *J Anal Toxicol.* 37 (2013) 652-658.
- [208] The Decree on Prescription of Medicines (STM 1088/2010), Ministry of Social Affairs and Health, Finland, <http://www.finlex.fi/fi/laki/alkup/2010/20101088>, accessed on May 15, 2014.
- [209] D.P. Alford, Chronic back pain with possible prescription opioid misuse, *JAMA.* 309 (2013) 919-925.
- [210] J.A. Gudin, S. Mogali, J.D. Jones, S.D. Comer, Risks, management, and monitoring of combination opioid, benzodiazepines, and/or alcohol use, *Postgrad Med.* 125 (2013) 115-130.
- [211] M. Sundström, A. Pelander, I. Ojanperä, Comparison between drug screening by immunoassay and ultra-high performance liquid chromatography/high-resolution time-of-flight mass spectrometry in post-mortem urine, *Drug Test Anal.* [Epub ahead of print] (2014).